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

**NCT number:** NCT03132922

**Document:** Statistical Analysis Plan

**Document Date:** 04 Jun 2019


# PROTOCOL NUMBER ADP-0044-001

# PHASE 1 DOSE ESCALATION, MULTI-TUMOR STUDY TO ASSESS THE SAFETY, TOLERABILITY AND ANTITUMOR ACTIVITY OF GENETICALLY ENGINEERED MAGE-A4$^{c1032}$T IN HLA-A2+ SUBJECTS WITH MAGE-A4 POSITIVE TUMORS

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: Phase 1 Dose Escalation, Multi-Tumor Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered MAGE-A4$^{c1032}$T in HLA-A2+ Subjects with MAGE-A4 Positive Tumors.

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 Good Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the MAGE-A4$^{c1032}$T Investigator Brochure.

| | |
|---|---|
| Investigator Name | |
| Investigator Title | |
| Investigator Site and Address | |
| Investigator Signature | |
| Date | |

# CLINICAL STUDY PROTOCOL

**Title:** Phase 1 Dose Escalation, Multi-tumor Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered MAGE-A4$^{c1032}$T in HLA-A2+ Subjects with MAGE-A4 Positive Tumors.

**Product Name:** MAGE-A4$^{c1032}$T

**Protocol Number:** ADP-0044-001

**Regulatory Agency Identifying Number:** 17235

**DATE OF ORIGINAL PROTOCOL: 23-NOV-2016**

| Amendment Number | Date | Reason for Change |
|---|---|---|
| 01 | 19-DEC-2016 | In response to FDA feedback the following changes have been made: inclusion criteria for creatinine clearance was modified to≥60 mL/min; a time frame for resolution of grade 4 thrombocytopenia was added; atezolizumab was added as a possible prior therapy for urothelial cancer subjects. |

| Amendment Number | Date | Reason for Change |
|---|---|---|
| 02 | 25July2017 | The following changes have been made to address requirements of Institutional Review Boards: addition of time period to DLT exclusions, removal of legally authorized representative.<br>Based on emerging data from Adaptimmune clinical trials the requirement for measurable disease prior to leukapheresis was removed to allow for T-Cell manufacture while the patient's disease is controlled.<br>The duration of wash-out periods for bridging therapies prior to leukapheresis and prior to lymphodepletion was adjusted based on better understanding of the effects of bridging therapy.<br>Revision of the brain metastasis exclusion criterion were made to better detail the eligibility criteria for patients with brain metastases. A brain CT/MRI was added for subjects with melanoma to reflect standard of care imaging practices.<br>Based on preclinical data demonstrating inactivity of the TCR with certain HLA alleles the eligibility criteria was updated to exclude HLA-A*02:07 and null alleles as sole HLA-A*02 alleles.<br>Corrections were made to: Table 4, steroid use, ECG and Table in section 16.3. Ranges were provided for the collection of tumor biopsies, and exosomes sampling.<br>Sponsor address and study physician information was updated. |
| 03 | 09March2018 | Addition of synovial sarcoma and myxoid/round cell liposarcoma subjects and increase of expansion group from 20 to 30 subjects at target dose. Addition of another dose of fludarabine in dose group 3 and optimization of lymphodepletion regimen.<br>Adjustments in urothelial and non-small cell lung cancer inclusion criteria. Changes in ranges of doses in dose escalation and expansion. Adjustment in exploratory objectives to reflect changes in technology and available assays. Adjustment of AE/SAE collection period to provide consistency across Adaptimmune Phase 1 trials and reflect current operationalization of the study. Administrative changes to correct inconsistencies. A detailed list can be found in Section 18. |

| Amendment Number | Date | Reason for Change |
|---|---|---|
| 04 | 24October2018 | Incorporated the Long Term Follow Up (LTFU) Phase into the protocol including Schedule of Procedures, and updated definitions regarding end of Interventional Phase and end of study.<br><br>Added adenocarcinoma sub-type for non-small cell lung cancer 5NSCLC) inclusion<br><br>Added section on supportive care guidance for encephalopathy syndrome (ES).<br><br>Updated supportive care guidance for cytokine release syndrome (CRS)<br><br>Added brain CT/MRI at Screening for subjects with melanoma and known brain metastases and required at Baseline now for all subjects.<br><br>Added second infusion option including eligibility criteria and schedules of procedures for a second infusion.<br><br>Deletion of Pharmacogenetics sample and analysis.<br><br>Incorporated Protocol clarification letter from: 20Jun2018<br><br>A detailed list of changes can be found in Section 18. |
| 05 | 29January2019 | Added language to change the lymphodepleting chemotherapy regimen for the Expansion Group.<br><br>Clarified the required collection time of CT/MRI scans.<br><br>Clarified size requirements for a tumor biopsy.<br><br>A detailed list of changes can be found in Section 18. |

| Amendment Number | Date | Reason for Change |
|---|---|---|
| 06 | 14March2019 | Increase in overall number of subjects to include additional subjects treated in the radiation substudy (ADP-0044-001R).<br>Increase in study enrollment duration<br>Clarified study endpoints are the same between the main study and substudy.<br>Remove PFT requirement from Exclusion #10.<br>Clarified language for second infusion.<br>Removed DLT exclusion.<br>Edited T cell infusion language.<br>Edited scan window.<br>Edited tumor biopsy requirements. |
| 07 | 04June2019 | Change lymphodepletion regimen, decrease in total cyclophosphamide dose<br>Updated baseline lab eligibility criteria: increase criteria for baseline ANC, Platelets and Creatinine<br>Added upper age limit cap of ≤75 years of age<br>Update exclusion criteria for uncontrolled intercurrent illness to include additional exclusions around history of cardiac disorders and stroke<br>Allow use of inhaled steroids and removed treatment restriction for respiratory disorders.<br>Updated Time and Events table to correspond with changes related to lymphodepletion regimen. |

## CONFIDENTIALITY STATEMENT

## DECLARATION

This study will be conducted in compliance with ICH 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]

## Responsible Study Physician/SAE Contact Information

| Role | Name | Day Phone and email | After hours phone | Fax Number |
|---|---|---|---|---|
| Primary Sponsor Study Physician | [redacted] | | | |
| Secondary Sponsor Study Physician | | | | |

## Sponsor Details

Adaptimmune LLC
351 Rouse Boulevard
Philadelphia, PA 19112
USA

# SYNOPSIS

| | |
|---|---|
| **Title:** Phase 1 Dose Escalation, Multi-tumor Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered MAGE-A4$^{c1032}$T in HLA-A2+ Subjects with MAGE-A4 Positive Tumors | |
| **Short Title** | MAGE-A4$^{c1032}$T for multiple tumor types |
| **Protocol Number** | ADP-0044-001 |
| **Phase** | 1 |
| **Methodology** | Phase 1 dose escalation followed by expansion to characterize safety and tolerability and assess antitumor activity across multiple tumor types. |
| **Study Duration** | This study will enroll for approximately 24 months and will be completed when the last subject has discontinued the study. |
| **Study Center(s)** | This is a multi-center study, including approximately 10 sites in the U.S. and Canada. Additional sites may be added at the discretion of the Sponsor, including sites in EU. |
| **Number of subjects** | Up to approximately 18 subjects in the dose escalation phase, up to approximately 30 subjects treated at the selected dose range inclusive of subjects accrued during the dose escalation phase to characterize safety and antitumor activity. Up to an additional 10 subjects will be treated in the ADP-0044-001R substudy at the selected dose range following lymphodepleting chemotherapy administered in combination with low dose radiation. Total number of treated subjects will be up to approximately 52. |

| **Objectives** | **Endpoints** |
|---|---|
| **Primary:**<br>To evaluate the safety and tolerability of autologous genetically modified T cells (MAGE-A4$^{c1032}$T) in subjects with HLA-A*02 and MAGE-A4 positive inoperable locally advanced or metastatic tumors | Adverse events (AEs), including serious adverse events (SAEs); laboratory assessments, including chemistry, hematology and coagulation.<br>Incidence of dose limiting toxicities (DLTs) and determination of optimally tolerated dose range.<br>Persistence of MAGE-A4$^{c1032}$T and replication-competent lentivirus (RCL) over time. |
| **Secondary:**<br>To evaluate the anti-tumor activity of initial infusion of autologous genetically modified T cells (MAGE-A4$^{c1032}$T) in HLA-A*02 subjects with MAGE-A4 positive inoperable locally advanced or metastatic tumors | Overall Response Rate (ORR) confirmed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1<br>Best overall response (BOR)<br>Time to response (TTR)<br>Duration of response (DoR)<br>Duration of stable disease (DoSD)<br>Progression free survival (PFS)<br>Overall survival (OS) |

| | |
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| **Secondary:** To evaluate potential gene therapy-related delayed adverse events for 15 years post infusion | • Presence of any of the following LTFU AEs:<br>• New malignancies<br>• New incidence or exacerbation of a pre-existing neurologic disorder<br>• New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder<br>• New incidence of a hematologic disorder<br>• Opportunistic and/or serious infections<br>• Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy<br>• And/or;<br>• Persistence of MAGE- A4$^{c1032}$ T and replication-competent lentivirus (RCL) over time. |
| **Exploratory:** [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| To evaluate the anti-tumor activity in subjects that receive a second infusion of autologous genetically modified T cells (MAGE-A4$^{c1032}$T) | ORR confirmed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for subjects who receive a second infusion |

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| **Inclusion /Exclusion Criteria** | Subjects will be assessed for eligibility prior to leukapheresis AND prior to lymphodepleting chemotherapy (unless otherwise noted) and must meet all specified criteria for study participation.<br><br>**Inclusion Criteria:**<br>A subject must meet the following inclusion criteria to be eligible for participation in this study:<br>1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH GCP guidelines and applicable local regulations.<br>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 and long term follow-up.<br>3. Subject is ≥18 to ≤75 years of age at the time of signing the study informed consent.<br>4. Subject has histologically confirmed diagnosis of any one of the following cancers: (A) urothelial cancer (transitional cell cancer of the bladder, ureter, urethra or renal pelvis), (B) melanoma, (C) squamous cell carcinoma of the head and neck, (D) ovarian cancer, (E) NSCLC (squamous, adenosquamous, adenocarcinoma, or large cell), (F) esophageal (squamous and adenocarcinoma) or (G) gastric cancer, (H) synovial sarcoma or (I) Myxoid/Round Cell Liposarcoma (MRCLS).<br>5. Subject has measurable disease according to RECIST v1.1 criteria prior to lymphodepletion. Measurable disease is not required prior to leukapheresis.<br>6. Subject has the following disease specific requirements for their tumor type (Note: there is no limit to the number of therapies prior to study entry):<br>• Inoperable or metastatic (advanced) urothelial cancer<br>– Has receivedat least one prior systemic therapy in the adjuvant or metastatic setting; may have received treatment with a PD-1/PD-L1 inhibitor.<br>• Inoperable or metastatic (advanced) melanoma<br>– Has received, is intolerant, or refused a CTLA-4 inhibitor (ipilimumab) or a PD-1 inhibitor (nivolumab or pembrolizumab) as monotherapy or a combination of ipilimumab and nivolumab.<br>– Has received or is intolerant of a BRAF inhibitor or the combination of BRAF and MEK inhibitors for BRAFv600 mutant melanoma.<br>• Inoperable or metastatic (advanced) squamous cell head and neck cancer<br>– Has received a platinum containing chemotherapy for treatment of primary tumor in adjuvant, locally advanced, or metastatic settings, is intolerant, or refused such treatment. May have received prior immunotherapy. |

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| | • Inoperable or metastatic (advanced) ovarian, primary peritoneal or fallopian tube carcinoma<br>– Has received platinum containing chemotherapy and has platinum refractory or resistant disease<br>– If platinum sensitive disease, should have received ≥2 lines of chemotherapy<br>– May have received PARP inhibitors, bevacizumab, or immunotherapy<br>• Histologically or cytologically confirmed diagnosis of advanced NSCLC (Stage IIIB or IV) or recurrent disease<br>– Has squamous cell, adenosquamous, adenocarcinoma, or large cell carcinoma.<br>– Subjects whose tumors are known to have EGFR mutations or ALK gene rearrangements must have failed (progressive disease or unacceptable toxicity) prior EGFR inhibitor or ALK tyrosine kinase inhibitor, respectively.<br>– Subjects with ROS-1 positive tumors must have failed an ALK inhibitor (crizotinib).<br>– Subject has received or is receiving at least one line of prior therapy<br>– May have received PD-1 inhibitors. There is no limit on lines of prior anti-cancer therapies.<br>• Inoperable or metastatic (advanced) squamous or adenocarcinoma of the esophagus, gastro-esophageal junction or gastric cancer<br>– Has received, is intolerant, or refused at least one 5-FU and/or platinum containing regimen.<br>– Subjects whose tumors are known to have Her2neu amplification must have failed (progressive disease or unacceptable toxicity) or refused trastuzumab.<br>– May have received ramucirumab.<br>• Subject has a diagnosis of advanced (metastatic or inoperable) synovial sarcoma or high grade myxoid liposarcoma / myxoid round cell liposarcoma confirmed by histology or cytogenetics.<br>– Subjects with synovial sarcoma must have previously received an anthracycline containing regimen. Subjects who are intolerant to anthracycline may have received ifosfamide alone.<br>– Subjects with MRCLS must have previously received or be intolerant to an anthracycline containing regimen.<br>7. Subject is HLA-A*02 positive. (This determination will be made under Screening Protocol ADP-0000-001). The Sponsor will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate subject eligibility based on HLA results.<br>8. Subject's tumor (either an archival specimen or a fresh biopsy) shows expression of the MAGE-A4 RNA or protein. All samples must have been reviewed by an Adaptimmune designated central laboratory |

confirming expression. (This determination will be made under Screening Protocol ADP-0000-001).

9. Subject has anticipated life expectancy> 6 months prior to leukapheresis and >3 months prior to lymphodepletion.
10. Subject has an ECOG Performance Status 0-1.
11. Subject has a left ventricular ejection fraction ≥50%.
12. Subject is fit for leukapheresis and has adequate venous access for the cell collection.
13. Female subject of childbearing potential (FCBP) must have a negative urine or serum pregnancy test. NOTE: FCBP is defined as premenopausal and not surgically sterilized. FCBP must agree to use maximally effective birth control or to abstain from heterosexual activity throughout the study, starting at the first dose of chemotherapy for 12 months after receiving the investigational product, or 4 months after there is no evidence of persistence/gene modified cells in the subject's blood, whichever is longer.

    OR

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

**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 |
| Hemoglobin | >80 g/L (without transfusion support within 7 days prior to leukapheresis) |
| **Coagulation** | |
| Prothrombin time or INR | ≤1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation. |
| Partial thromboplastin time (PTT) | ≤1.5x (ULN) unless receiving therapeutic anticoagulation. |
| **Renal** | |
| Calculated or measured creatinine clearance [1] | ≥ 60 mL/min<br>Exception: Subjects with urothelial cancer ≥40 mL/min |
| **Hepatic** | |

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| Serum total bilirubin | ≤1.5 x ULN (unless subject had documented Gilbert's Syndrome) |
| Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT) | ≤2.5x 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 EDTA GFR measurement, according to standard practice at the treating institution.
Renal function will be reassessed at Baseline.

**Exclusion Criteria:**

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

1. HLA-A genotype (The Sponsor will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate subject eligibility based on HLA results):
   - Subject is HLA-A*02:05 positive in either allele.
   - Subject has HLA-A*02:07 as the sole HLA-A*02 allele (eg, a subject with HLA alleles A*02:04 and A*02:07 is eligible)
   - Subject has any A*02 null allele (designated with an "N", eg, A*02:32N) as the sole HLA-A*02 allele
2. Subject has received or plans to receive the following excluded therapy/treatment: prior to leukapheresis or lymphodepleting chemotherapy:

| **Treatment/Therapy** | **Required Wash-out Prior to Leukapheresis** | **Required Wash-out Prior to Lymphodepletion** |
|---|---|---|
| Cytotoxic chemotherapy | 3 weeks | 3 weeks |
| Small Molecules/Tyrosine kinase inhibitor (TKI) such as dabrafenib, trametinib, vemurafaneb and cobimetinib. NOTE: No washout period is required for compounds that do not cause bone marrow suppression/lymphopenia or for EGFR and ALK/ROS-1 inhibitors unless the multi-kinase inhibitor targets VEGFR (e.g. afatinib), PDGFR or cKit receptors | 1 week | 1 week |

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| Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors, biologics) | 2 weeks | 2 weeks |
| Experimental anti-cancer Vaccine | N/A | 2 months in the absence of tumor response.<br>The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months |
| Gene therapy using an integrating vector | Any use of previous gene therapy using an integrating vector is not permitted | Any use of previous gene therapy using an integrating vector is not permitted |
| Corticosteroids or any other immunosuppressive therapy.<br>NOTE: Use of topical steroids and inhaled steroids are not an exclusion. See Section 6.1 for exceptions. | 2 weeks | 2 weeks |
| Investigational treatment | 2 weeks or 5 half-lives, whichever is shorter | 2 weeks or 5 half-lives, whichever is shorter |
| Radiotherapy that involves the lung (V20 exceeding 30% lung volume) or pericardium (>20Gy). NOTE: Exception for a lesser dose or 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. | N/A | 3 months |
| Radiation to vital organs (e.g. liver, kidney) | N/A | 4 weeks |
| Radiation to the pelvis | 4 weeks | 4 weeks |
| Whole Brain Radiotherapy (WBRT) or Brain Stereotactic Radiosurgery (SRS) | N/A | 2 weeks |

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| Radiotherapy to the target lesions | N/A | 3 months prior to lymphodepleting chemotherapy. A lesion with unequivocal progression may be considered a target lesion. (Note: there is no washout period for palliative radiation to non-target organs). |
| NOTE: Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician | | |

3. Subject that has toxicity from previous anti-cancer therapy must have recovered to ≤Grade 1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible e.g. peripheral neuropathy) can be enrolled.
4. Subject has history of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study.
5. Subject has history of chronic or recurrent (within the last year prior to Screening) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments, including anti-TNF agents.
6. Subject had major surgery within 4 weeks prior to lymphodepletion; subjects should have been fully recovered from any surgical related toxicities.
7. Subject has symptomatic CNS metastases. Subject with a prior history of symptomatic CNS metastases must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiation (WBRT) or surgery) and be neurologically stable for at least 1 month, not requiring anti-seizure medications and off steroids for at least 14 days prior to leukapheresis and lymphodepletion. Subject who has asymptomatic CNS metastatic disease without associated edema, shift, requirement for steroids or anti-seizure medications for the treatment of seizures are eligible. 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.
8. Subject has any other active malignancy besides the tumor under study within 3 years prior to Screening. Exceptions: adequately-treated malignancies not likely to require therapy (e.g., completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma). Newly identified prostate cancers found during cytoprostatectomy are

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| | permitted. Subjects must be in complete remission from prior malignancy in order to be eligible to enter the study.<br>9. Subject has an electrocardiogram (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 [BBB]) over 3 consecutive ECGs. Either Fridericia's or Bazett's formula may be used to correct the QT interval.<br>10. Subject has uncontrolled intercurrent illness including, but not limited to:<br>• Ongoing or active infection<br>• Clinically significant cardiac disease defined by CHF New York Heart Association (NYHA) >Class1; uncontrolled clinically significant arrhythmia in last 6 months; acute coronary syndrome (ACS) (angina or myocardial infarction) in last 6 months<br>• Interstitial lung disease (pneumonitis), history of pneumonectomy, or of COPD with ≥ one exacerbation within 1 year prior to the Screening Visit that required treatment with systemic corticosteroids or resulted in hospitalization,<br>• Pre-existing active skin disorders of Grade 2 or greater severity.<br>• Current uncontrolled hypertension despite optimal medical therapy.<br>• History of stroke or central nervous system bleeding, transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) within last 6 months<br>11. Subjects who in the opinion of the Investigator will be unlikely to fully comply with protocol requirements.<br>12. Subject has active infection with HIV, HBV, HCV or HTLV as defined below:<br>• Positive serology for HIV<br>• Positive HBV surface antigen test. Positive HBV DNA test. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months.<br>• Positive hepatitis C RNA test. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value<br>• Positive serology for HTLV 1 or 2.<br>Re-screening for infectious disease markers is not required at Baseline (prior to lymphodepletion).<br>13. Subject is pregnant or breastfeeding. |

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| **Investigational Product, Dose, Route, Regimen** | The investigational product is MAGE-A4$^{c1032}$T administered by infusion following lymphodepleting chemotherapy. The initial dose selected for MAGE-A4$^{c1032}$T is 0.1x10$^9$ transduced cells to be escalated to 1 x 10$^9$ and then to 5 x10$^9$ transduced cells in a modified 3 + 3 dose escalation scheme. 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 30 subjects in the Expansion Group and up to 10 additional subjects in the ADP-0044-001R substudy populations). A second infusion of MAGE-A4$^{c1032}$T cells may only be given to eligible subjects following a confirmed response (CR or PR) or clinical benefit ≥ 6 weeks after the first T-cell infusion and whose tumor continues to express the appropriate antigen target. |
| **Comparator therapy** | None |
| **Statistical Methodology** | Data from the main study and sub-study will be analyzed separately and overall.<br>Descriptive statistics will be conducted for safety and anti-tumor activity. Bayesian predictive probabilities for DLT will be used to provide safety oversight as subjects are enrolled at the target dose range during the expansion phase.<br>Safety and demographic data will be summarized by cell dose group. Continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.<br>All adverse events 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 cell dose group. AEs will be tabulated by severity, relationship to treatment and seriousness.<br>ORR will be summarized by two-sided 95% Wilson and exact confidence intervals in each dose group. 95% credible intervals will also be used to describe the ORR in the expansion cell dose group.<br>The endpoints BOR, TTR, DoR, DoSD, PFS and OS will be summarized descriptively. In the expansion cell dose group, time to event endpoints will be summarized and displayed graphically using Kaplan-Meier (K-M) methodology to estimate the median, and the 25th and 75th percentiles. Overall Survival will be assessed at fixed time points such as 1 year and 2 years using K-M methods.<br>In addition the safety, demography and anti-tumor data may be presented combining the cell dose groups that encompass the selected target dose range. |

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# 1. BACKGROUND AND STUDY RATIONALE

## 1.1. 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; Rosenberg, 2015].

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 [Dudley, 2005; Besser, 2010]. This therapy, however, has been limited by the requisite surgery to procure tumor-reactive TILs, 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 the majority of tumor antigens are normally expressed self-antigens. Hence, the natural T cell receptors (TCRs) that recognize self-tumor antigens may be 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 immune activation 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 reduced expression of antigen and also decreased expression of major histocompatibility complex (MHC) class I molecules [Marincola, 2000; Baccala, 2005; Barrett, 2009].

Gene-transfer-based strategies have therefore been developed to overcome the consequences of immune tolerance on the tumor-specific T cell repertoire. These approaches provide the potential to redirect T cells to effectively target tumors by the transfer of antigen-specific affinity-optimized 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. TCR-based engineering approaches have certain inherent biological advantages, most notably that the vast

majority of cellular proteins can be targeted because the approach is not limited to the targeting of cell surface epitopes as is the case for chimeric antigen receptors (CAR), 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-A4$^{c1032}$T Investigator Brochure.

## 1.2. Cancer Testis Antigen Expression in Cancer

The cancer/testis antigens (CTA) comprise a number of genes that have restricted expression to the testis, but have been identified by their expression in various tumor types [Caballero, 2009]. These include NY-ESO-1, MAGE-A family, SSX2, BAGE, GAGE, and CT7 among others. Most of these testis-specific genes are coded on the X chromosome. It should be noted that several of these antigens, including MAGE-A3, MAGE-A10 and MAGE-A8, also have expression in placenta [Caballero, 2009]. In general, melanoma, ovarian cancer and lung cancer, particularly of the squamous cell type, have the highest frequency of RNA expression across the CTAs. Epithelial cancers such as breast, bladder and prostate cancer have intermediate expression, with frequency of mRNA expression in the range of 30% to 50%. MAGE-A4 has been described as having expression in 82% of synovial sarcoma by Immunohistochemistry (IHC). High expression of NY-ESO-1 and MAGE-A4 was significantly correlated with the presence of necrosis and advanced clinical stage [Iura 2017a]. A further report suggests that 67.7% of myxoid liposarcomas, express MAGE-A4 [Iura 2017b]. The CTAs often have coordinated expression, with several expressed in a single tumor [Gure, 2005]. While it is generally seen that mRNA expression of these antigens correlates well with protein expression it should be noted that there is frequently heterogeneous expression of protein across the tumor, with strong expression in a small subset of tumor cells. There is also epigenetic and post-transcriptional modification that determines protein expression levels under certain conditions, as well.

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

Some CTAs, such as NY-ESO-1, SSX, MAGE-A1, MAGE-A3and MAGE-A10, have been shown to elicit humoral or cell mediated immune responses [Daudi, 2014]. The approach used

here redirects T cells to effectively target tumors by the transduction of antigen-specific high-affinity TCR.

## 1.3. Current Treatment Options for Cancers Expressing MAGE- A4

The CTA MAGE-A4 is expressed to varying frequencies in the following cancers: urothelial (bladder) cancer, melanoma, head and neck cancer, ovarian cancer, non-small cell lung cancer (NSCLC), esophageal cancer, gastric cancer, synovial sarcoma or myxoid/round cell liposarcoma (MRCLS), and have therefore been selected for this Phase 1 dose escalation study. Four of these cancers are associated with environmental carcinogens or pathogens (e.g., sun exposure, smoking, human papilloma virus), have a high nonsynonymous mutation burden, and are responsive to immunotherapeutic modalities (NSCLC, urothelial, melanoma, head and neck). Although the overall tumor mutational burden has been associated with improved efficacy of immunotherapy, it remains unclear how specific mutational properties are associated with neoantigen presentation and response to immunotherapy. The current and emerging treatment options are briefly summarized (not meant to be a comprehensive overview) in the subsections below. The overall response rate (ORR) in second line therapy and beyond for the populations proposed in this study ranges from 10-30%.

***Urothelial Cancer***

In the US, the incidence and mortality of urothelial cancer are approximately 77,000 and 16,000 annually respectively. Ninety percent of urothelial cancers originate in the bladder, while 8% originate in the renal pelvis and 2% in the ureter or urethra. Non-muscle invasive urothelial bladder cancer (UBC) comprises 70% of newly diagnosed bladder cancers and is generally treated with transurethral resection of the bladder tumor (TURBT) with or without intravesical Bacillus Camille Guerin (BCG) immunotherapy or intravesical chemotherapy. The rate of recurrence within 5 years for patients with tumors confined to the mucosa and submucosa is approximately 31% to 78% respectively. Radical cystectomy is the standard treatment for muscle invasive bladder cancer. A meta-analysis has shown adjuvant platinum-based chemotherapy to improve survival in muscle invasive bladder cancer [Advanced Bladder Cancer Collaboration, 2005].

The average survival for metastatic urothelial bladder cancer (mUBC) is 12 to 15 months. Combination chemotherapy regimens are the primary treatment for metastatic bladder cancer: commonly used regimens are gemcitabine with cisplatin or carboplatin or MVAC (methotrexate, vinblastine, Adriamycin, cisplatin) [Loehrer, 1992; Saxman, 1997]. Several cytotoxic agents and small molecule inhibitors have been investigated as second-line therapies and have limited activity [Dreicer, 2004; De Santis, 2012].

The FDA approved atezolizumab (PD-L1 inhibitor) for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease had worsened during or following platinum-containing chemotherapy based on a single arm trial. The ORR was 14.8% in the overall study population. In patients who were PD-L1 positive (expression on tumor-infiltrating immune cells), the ORR was 26% compared to 9.5% in those who were PD-L1 negative. A Phase 3 study comparing atezolizumab to physician's choice chemotherapies in patients who

have failed platinum containing therapy is on-going [NCT02302807]. In a Phase 1b study of pembrolizumab in patients with heavily pretreated metastatic bladder cancer the 12-month progression free survival (PFS) was 19% with ORR in patients with PD-L1 positive tumors of 38% [Plimack, 2015]. A Phase 3 clinical trial is being conducted [NCT02256436]. Oncogenic viruses and ACTs are some of the other immunotherapies being evaluated in UBC.

***Melanoma***

In the US, the incidence and mortality are approximately 77,000 and 10,000 annually respectively. Treatment for melanoma is changing rapidly with advances in both targeted therapy and immunotherapy. Adjuvant pegylated interferon alpha-2b has been shown to prolong recurrent free survival in patients with Stage III melanoma [Eggermont, 2008]. The checkpoint inhibitor, ipilimumab has recently demonstrated significant improvement in recurrence free survival when used as adjuvant therapy after surgery [Eggermont, 2015]. Talimogene laherparepvec (Imlygic), an oncolytic virus that is injected directly in to the tumors resulted in higher durable responses and overall survival (OS) compared to granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with unresectable Stage III and IV melanoma [Andtbacka, 2015].

Ipilumumab [Hodi, 2010], nivolumab [Weber, 2015], and pembrolizumab [Ribas, 2015] are approved for the treatment of patients with metastatic melanoma. The use of these immuno-oncology drugs as single agents and more recently in combinations is rapidly changing the treatment of metastatic melanoma. In previously untreated patients with metastatic melanoma, nivolumab (anti-PD-1) alone or combined with ipilumumab resulted in significantly longer PFS than ipilumumab alone. In patients with PD-L1–negative tumors, the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone [Larkin, 2015]. The ORR and PFS associated with the combination of nivolumab and ipilumumab were also substantially higher than those with ipilimumab alone in both BRAF wild type and BRAF mutant melanoma [Postow, 2015].

About half of all melanomas harbor an activating mutation in the BRAF gene. BRAF inhibitors, vemurafenib and dabrafenib were each approved initially as monotherapies for the treatment of patients with BRAFv600E mutation positive metastatic melanoma based on the results of randomized trials against dacarbazine [Chapman, 2011; Hauschild, 2012]. Improved efficacy was subsequently demonstrated with the combination of a BRAF inhibitor with a MEK inhibitor. The combination of dabrafenib plus trametinib significantly improved OS in previously untreated patients with metastatic melanoma with *BRAF* V600E or V600K mutations, as compared with dabrafenib monotherapy [Robert, 2015]. Similarly the combination of vemurafenib and cobimetinib demonstrated an improvement in OS compared to vemurafenib monotherapy [Wongchenko, 2015].

***Head and Neck Cancer***

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

Loss of chromosomal region or heterozygosity, or microsatellite instability, are common genetic changes and occur from early stages in the progression of these tumors. Over the past 30 years, there has been a drop in the incidence of head and neck cancers caused by tobacco and alcohol, and a rise in the incidence of head and neck cancers caused by HPV; up to 70% of tumors of the oropharynx are predicted to be due to HPV-16/18 infection. In the US, the incidence and mortality of cancers of the head and neck are 62,000 and 13,000 respectively.

The majority of patients with head and neck cancer present with locally advanced disease. Those who present with early Stage I and II disease are often treated with either radiation or surgery and have excellent prognosis. For those patients with Stage III/IV locally advanced squamous cell carcinoma of the head and neck (SCCHN) , the relapse and 3-year survival rates following surgery and/or radiotherapy (RT) with or without chemotherapy are 40% to 60% and 30 to 50% respectively [Posner, 2007]. The addition of adjuvant chemotherapy in a large Phase 3 trial found no difference in survival [Cooper, 2004]. Bolus cisplatin every three weeks during radiation is often used in patients with advanced disease [Bernier, 2004; Cooper, 2004].

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

Multiple trials are underway in SCCHN with PD-1 and PD-L1 inhibitors with encouraging data being reported. A clinical study of pembrolizumab demonstrated clinical activity in patients with recurrent/metastatic SCCHN enriched for PD-L1 positive tumors with a response rate of 20%. An expansion cohort of patients with advanced recurrent or metastatic SCCHN irrespective of PD-L1 expression or HPV status who received a fixed dose of pembrolizumab in 99 evaluable patients demonstrated an ORR of 18.2% with 18% partial response (PR) and 31% stable disease (SD) [Siewert, 2015]. Pembrolizumab has been approved by FDA for patients with recurrent or metastatic disease after failure of platinum-containing chemotherapy. Nivolumab was reported to increase median OS in both HPV-positive and HPV-negative patients with recurrent or metastatic SCCHN that progressed after platinum-based chemotherapy compared with single-agent Investigator's choice chemotherapy [Gillison, 2016].

***Ovarian Cancer***

Ovarian, fallopian tube, or primary peritoneal cancer have a common derivation from the Müllerian epithelium; they generally follow a similar clinical course with a pattern of peritoneal spread, and are treated following similar approaches. In the US, the incidence and mortality of these cancers are approximately 22,000 and 14,000 annually, respectively. Over half the cases occur in women older than 65. The most common histologic subtype is high-grade serous ovarian cancer. Clear cell, endometrioid and mucinous have different gene-expression signatures [Birrer, 2010]. Stromal and germ cell tumors are relatively uncommon and comprise fewer than 10% of cases. Approximately 20% of ovarian cancer cases have a familial etiology, with BRCA1 and BRCA2 being the 2 most commonly involved genes [Lynch, 1993;

Pennington, 2012]. In women with germline mutations of BRCA genes, prophylactic oophorectomy confers a 90% reduction in the risk of ovarian cancer [Rebbeck, 2002].

Most patients present with advanced disease, including nodal and intraperitoneal involvement, particularly in the case of high grade serous carcinomas. Radical hysterectomy, bilateral oophorectomy and optimal cytoreduction are the goals of the initial surgical treatment. Relapse in Stage I is associated with grade and histology; most patients with serous subtype present with Stages III or IV. Following resection, patients with advanced or metastatic disease generally receive treatment with platinum and taxanes as first line chemotherapy. PARP inhibitors block PARP activity thereby preventing single strand DNA repair. In patients who have homologous recombination repair deficiency due to BRCA inactivating mutations, PARP inhibition results in cell lethality. Case-control studies suggest that, as a result of deficit in DNA repair mechanisms, patients with BRCA1 and BRCA2 mutations may respond better to chemotherapy compared to patients with sporadic ovarian cancer. The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib is approved for patients with ovarian cancer and BRCA mutations who have received prior chemotherapy.

Approximately 80% of patients relapse after first line platinum and taxane based chemotherapy. Studies have shown that neither second-look laparotomies nor early detection of recurrence by serial CA-125 measurements improve survival. Patients whose tumors recur after 6 months following completion of platinum based chemotherapy are generally treated with additional platinum based therapy. Patients who progress during treatment or within 6 months of treatment cessation are thought to have platinum refractory or resistant disease and are generally not candidates for further platinum based therapies. Patients with BRCA mutations may be treated with the PARP inhibitor olaparib. Patients without BRCA mutations may be treated with drugs such as pegylated liposomal doxorubicin, gemcitabine, topotecan or taxanes. The VEGF inhibitor bevacizumab is approved for patients with platinum resistant, recurrent ovarian cancer in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin. There is a clear unmet need for new therapies for patients with platinum resistant ovarian cancer.

***Non-Small Cell Lung Cancer (NSCLC)***

Lung cancer is the third most common form of the disease in the US after prostate cancer in men and breast cancer in women. It is estimated that approximately 224,000 new cases will be diagnosed in 2016 accounting for about 13% of all cancer diagnoses [Cancer Facts and Figures, 2016]. Lung cancer is the leading cause of cancer deaths in both men and women (about 27%) and it is estimated that there will be approximately 158,000 deaths from lung cancer in the US in 2014. Overall, since 1990, death rates have fallen in men but increased slightly in women according to a recent review of world-wide cancer incidence [Torre, 2016]. The 1-year and 5-year survival rates for lung cancer during 2003 to 2009 were 43% and 17% respectively. One reason for the relatively poor prognosis is initial diagnosis with advanced disease (only 15% of lung cancers are diagnosed at a localized stage).

NSCLC accounts for 84% of lung cancer and may be classified according to histology as adenocarcinoma (40%), which usually originates in peripheral lung tissue; squamous-cell carcinoma (25%) typically occurring close to large airways; and large cell carcinoma (10%)

[NIH, 2016]. Subsets of adenocarcinomas can be further defined at the molecular level by the specific mutations of genes coding, for example, for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase receptor (ALK).

For early stage NSCLC surgery is the treatment of choice, followed by adjuvant chemotherapy. Chemoradiation alone or followed by surgery is commonly used for Stage IIIA NSCLC. For patients with advanced NSCLC (Stages IIIB and IV), recommended [NCCN, 2016] first line treatment is with platinum-based doublet chemotherapy. This generally consists of cisplatin or carboplatin with another cytotoxic agent (pemetrexed, taxanes, gemcitabine, vinorelbine or camptothecins). Other agents such as bevacizumab or cetuximab may be added to the regimen. Erlotinib and afatinib are indicated for patients whose tumors contain sensitizing EGFR mutations and crizotinib is indicated in patients whose tumors contain ALK or ROS1 rearrangements. In patients who experience disease progression after primary therapy, single agent chemotherapy or appropriate targeted drugs may be indicated as second or third line therapy. Recently PD-1 inhibitors have demonstrated activity in metastatic NSCLC. Both pembrolizumab and nivolumab have been approved by FDA as monotherapy for patients with disease progression after cisplatin based therapy or after targeted therapy if the tumors contain EGFR or ALK alterations.

***Esophageal and Gastric Cancer***

In Western countries, the incidence of adenocarcinoma of the esophagus is rising rapidly, while the incidence of squamous cell carcinoma of the esophagus is declining owing to a decrease in tobacco use. The combined incidence and mortality of esophageal and gastric cancers in the US are 43,000 and 26,400 cases respectively. Unfortunately many patients present with advanced disease, a stage associated with 5 year survival of only 5% to 15% and median survival of 8 to 10 months. The mainstay of treatment for advanced disease is fluoropyrimidine and platinum based combination chemotherapy. Low response rates and high levels of toxicity are observed with second-line chemotherapy. Trastuzumab prolongs survival in patients with Her2-neu expressing gastric cancer (10 to 30% of gastric cancer). There is some evidence that oesophagogastric cancer can respond to immunotherapy [Kim, 2005; Popiela, 2004; Ralph, 2010], but no other treatments beyond palliative chemotherapy are available for patients with advanced disease. There is an unmet need for patients with advanced disease who have progressed after first line therapy. Oesophagogastric cancer expresses MAGE-A4, both squamous cell cancers and adenocarcinomas, and tumors of both primary sites and histologies will be included in this trial.

***Synovial Sarcoma and Myxoid/Round Cell Liposarcoma***

Sarcomas are rare malignant tumors originating from mesenchymal cells and their precursors, and represent ~1% of all cancers in adults worldwide each year (10% of cancers in children, and 8% of cancers in adolescents) and ~2% of cancer related mortality [Singer, 2000; Amankwah, 2013]. The estimated international incidence rates of soft tissue sarcoma ranges between 4 and 6 cases per 100,000 per year [Stiller, 2012; Ferrari, 2011]. Soft tissue sarcomas consist of approximately 50 different histological subtypes.

### *Synovial Sarcoma*

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

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

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

Clinical trials investigating the efficacy and safety of adoptive T cell therapy are ongoing and have demonstrated evidence of clinical efficacy. In an open label non-randomized multi-cohort pilot study of genetically engineered NY-ESO-1 SPEAR T-Cells in HLA-A2$^{+}$ patients with synovial sarcoma (NCT01343043) in the first Cohort confirmed responses (1 CR and 5 PR) were observed in 6 of 12 (50%) subjects that received NY-ESO-1$^{c259}$T. The median duration of response (DOR) was approximately 31 weeks with a range of 13 weeks-72 weeks [D'Angelo, 2017]. There is an unmet need for patients with advanced disease who have progressed after first line therapy. This data supports the continued study of TCR therapies in synovial sarcoma. Patients with advanced disease will be included in this trial

### *Myxoid/Round Cell liposarcoma (MRCLS)*

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

Treatment involves the wide surgical excision of the tumor and surrounding tissue and high grade round cell liposarcoma may be treated with pre-operative chemotherapy and/or pre-operative or post-operative radiotherapy [NCCN, 2012]. Doxorubicin and ifosfamide are the first line systemic treatment options for patients with metastatic disease. Retrospective analyses in previously untreated patients demonstrated response rates of ~38 - 45% [Jones, 2005; Katz, 2012]. Once patients relapse or develop metastatic disease treatment is aimed at slowing that

pace of progression. A variety of therapies are used in the second-line setting and beyond although only trabectedin and eribulin are approved. Despite the approval of these two agents, overall survival in patients with relapsed disease remains 12-13 months [Demetri, 2016; Schoffski, 2016]. There is an unmet need for patients with advanced disease who have progressed after first line therapy. Subjects with advanced (metastatic or inoperable) high grade MRCLS whose tumors express MAGE-A4 will be included in this study.

## 1.4. Discovery of MAGE-A4$^{c1032}$T

Several peptides derived from MAGE proteins have been identified by mass spectroscopy from tumor cell lines, including the human leukocyte antigen (HLA) HLA-A*02-restricted peptide MAGE-A4230-239; GVYDGREHTV. HLA class I molecules are involved in the presentation of antigenic peptides on tumors to T lymphocytes. The prevalence of HLA subtypes varies from population to population, the most common in the western world being HLA-A2. Among the HLA-A2 allelic variants, the most prevalent are HLA-A*02:01 (approximately 45% of Caucasian and Hispanic population) and HLA-A*02:06 (www.allelefrequencies.net). Adaptimmune generated 20 parental TCRs that recognize the HLA-A*02-restricted MAGE-A4 peptide GVYDGREHTV. From these, one demonstrated some response toward natively MAGE-B2 and MAGE-A4-positive cell lines and was selected for engineering, resulting in 17 enhanced affinity TCRs that were tested in cellular assays against MAGE-A4 positive and negative cell lines and primary cells. Cellular testing for potency and specificity identified ADB1032 as being optimal, demonstrating enhanced potency against MAGE-A4 positive tumor cell lines, while retaining a favorable specificity and safety profile.

The Investigational Medicinal Product (IMP) is comprised of autologous CD4 and CD8 T cells obtained from eligible subjects who have MAGE-A4 expressing tumors and who are HLA-A*02 positive. Patients who are HLA-A*02:05 are excluded because alloreactivity has been observed in vitro with MAGE-A4$^{c1032}$T to this HLA allele. Patients with either HLA-A*02:07 or any A*02 null allele as the sole HLA-A*02 allele are excluded due to inactivity with these alleles. The T cells undergo self-inactivating (SIN) lentiviral transduction with MAGE-A4$^{c1032}$T specific nucleic acid under GMP conditions. The resulting polyclonal MAGE-A4$^{c1032}$T specific peptide enhanced affinity receptor (SPEAR) T are now genetically engineered to target the antigen on the subject's MAGE-A4 positive advanced tumor.

## 1.5. Study Design

This study is designed as a dose escalation trial with expansion up to 30 subjects at the selected dose range (inclusive of those treated during dose escalation at the same dose). The dose escalation stage of the study will test up to 3 cell doses in a modified 3 + 3 escalation design. Up to an additional 10 subjects will be treated in a substudy (ADP-0044-001R) at the selected dose range following lymphodepleting chemotherapy administered in combination with low dose radiation. Eligible subjects will have appropriate HLA-A and inoperable or metastatic tumors expressing the MAGE-A4 antigen. Subjects with the following tumor types will be eligible for enrollment: urothelial, melanoma, head and neck (squamous), ovarian, NSCLC (squamous, adenosquamous, adenocarcinoma, or large cell), esophageal (squamous and adenocarcinoma),

gastric, synovial sarcoma or MRCLS. These tumor types were selected based on the expression profiles of MAGE-A4 RNA and protein. The frequency of RNA expression reported in the Cancer Genome Atlas sequencing database ranges from 20% in esophageal adenocarcinoma to 60% in squamous cell lung cancer. Adaptimmune's analysis of MAGE-A4 RNA expression detected by quantitative polymerase chain reaction (qPCR) ranged from 10% to 60%. Subjects who have a confirmed response (CR or PR) or clinica benefit ≥ 6 weeks after the first T-cell infusion and whose tumor continues to express the appropriate antigen target may be eligible for a second infusion.

### 1.5.1. 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. In a multi cohort clinical study of NY-ESO T-cells in subjects with advanced synovial sarcoma (ClinicalTrials.gov Identifier: NCT01343043, different lymphodepleting regimens were under investigated. In Cohort 1, lymphodepletion consisted of cyclophosphamide 1800 mg/m$^2$/day for 2 days plus fludarabine 30 mg/m$^2$/day for 4 days and this demonstrated anti-tumor activity with 6 of 12 treated subjects having an objective response (1CR, 5 PR).

In Cohort 4 lymphodepletion is reduced and consisted of cyclophosphamide 600 mg/m$^2$/day and fludarabine 30 mg/m$^2$/day both for 3 days and this also demonstrated objective tumor responses in 4 of 15 subjects. Treatment has been well tolerated in both cohorts (D'Angelo, 2018b).

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.

Responses were achieved in both Cohort 1 and Cohort 4, however, 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 (19,650 vector copies/µg) when compared to Cohort 1 (76,793 vector copies/µg), despite similar transduced cell doses in the two cohorts (D'Angelo, 2018b). The data indicate that higher dose lymphodepletion is needed to achieve optimal post infusion peak expansion and durable responses.

A third cohort in this study evaluated a lymphodepletion regimen of cyclophosphamide alone (1800mg/m$^2$ x 2 days) and demonstrated an objective response in 1 of 5 treated subjects. Data from this study suggests that fludarabine is an important component of T-cell lymphodepleting regimens and fludarabine 30 mg/m$^2$ given daily for 4 days in combination with

cyclophosphamide may be associated with more objective responses (the CAR-T product tisagenlecleucel, recently approved by the FDA, also utilizes fludarabine 30 mg/m$^2$ for 4 days in combination with cyclophosphamide). In summary, the safety coupled with the efficacy data in this study support the use of a lymphodepletion regimen consisting of cyclophosphamide 1800 mg/m2/day for 2 days plus fludarabine 30 mg/m2/day for 4 days.

In this dose escalation study, the lymphodepleting regimen in Group 1 and Group 2 will evaluate cyclophosphamide 600mg/m$^2$ and fludarabine 30 mg/m$^2$ together for 3 days. Once safety is established in this study population, the fludarabine in the lymphodepletion regimen will be increased in Group 3 to 30 mg/m$^2$ for 4 days with cyclophosphamide 600mg/m$^2$ for 3 days. After safety was established in Group 3 a lymphodepletion regimen of cyclophosphamide 1800 mg/m$^2$ for 2 days and fludarabine 30mg/m$^2$ for 4 days was implemented and administered to seven subjects in the expansion phase. Due to safety reports of prolonged pancytopenia with bone marrow hypoplasia the cyclophosphamide dose is being reduced. 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.

With the implementation of this Amendment (07) the study will revert back to the Group 3 lymphodepletion regimen for the remainder of the Expansion Group and in the sub study population.

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

# 2. TRIAL OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory endpoints listed below are applicable to both this study (ADP-0044-001) and the sub study (ADP-0044-001R).

| Objectives | Endpoints |
|---|---|
| **Primary:** | |
| To evaluate the safety and tolerability of autologous genetically modified T cells (MAGE-A4$^{c1032}$T) in subjects with HLA-A*02 and MAGE-A4 positive inoperable locally advanced or metastatic tumors | Adverse events (AEs), including serious adverse events (SAEs); laboratory assessments, including chemistry, hematology and coagulation<br>Incidence of dose limiting toxicities (DLTs) and determination of optimally tolerated dose range<br>Persistence of MAGE-A4$^{c1032}$T and replication-competent lentivirus (RCL) over time |
| **Secondary:** | |
| To evaluate the anti-tumor activity of initial infusion of autologous genetically modified T cells (MAGE-A4$^{c1032}$T) in HLA-A*02 subjects with MAGE-A4 positive inoperable locally advanced or metastatic tumors | • Overall Response Rate (ORR) confirmed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1<br>• Best overall response (BOR)<br>• Time to Response (TTR)<br>• Duration of Response (DoR)<br>• Duration of Stable Disease (DoSD)<br>• Progression Free Survival (PFS)<br>• 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:<br>• New malignancies<br>• New incidence or exacerbation of a pre-existing neurologic disorder<br>• New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder<br>• New incidence of a hematologic disorder<br>• Opportunistic and/or serious infections<br>• Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy and/or;<br>  • Persistence of MAGE-A4$^{c1032}$T and replication-competent lentivirus (RCL) over time. |

| **Exploratory** | |
|---|---|
| To evaluate the persistence, phenotype and functionality of transduced (MAGE-A4$^{c1032}$T) and non-transduced T cells | Correlate persistence, phenotype and functionality of transduced (MAGE-A4$^{c1032}$T) and non-transduced T cells in the peripheral blood and/or tumor with response to treatment and safety |
| Characterize the tumor and tumor microenvironment pre and post- T cell infusion to understand tumor driven determinants of response and resistance to MAGE-A4$^{c1032}$T therapy | Determination of target antigen expression, genes related to antigen processing/presentation, and cell surface co-stimulatory ligands |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| To evaluate the anti-tumor activity in subjects that receive a second infusion of autologous genetically modified T cells (MAGE-A4$^{c1032}$T) | ORR confirmed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for subjects who receive a second infusion |

# 3. INVESTIGATIONAL PLAN

## 3.1. Overall Study Design

This Phase 1 study is designed as a cell dose escalation trial in HLA-A*02 subjects with MAGE-A4 positive locally advanced inoperable or metastatic cancer of the following types: urothelial, melanoma, head and neck (squamous cell), ovarian, NSCLC (squamous, adenosquamous, adenocarcinoma, or large cell), esophageal (squamous and adenocarcinoma), gastric, synovial sarcoma or MRCLS. The study will enroll approximately 18 subjects with inoperable or metastatic (advanced) cancers of these types in the dose escalation phase. The study will enroll subjects using a modified 3 + 3 cell dose escalation design to evaluate DLTs and determine the target cell dose range (Section 3.2.5 and Section 3.3). Following the dose escalation phase the study will be expanded to enroll up to approximately 30 subjects at the selected dose range (inclusive of those treated during dose escalation at that dose range) across all the eligible tumor types to better characterize and assess overall safety. Up to an additional 10 subjects will be treated in the sub study (ADP-0044-001R) at the selected dose range following lymphodepleting chemotherapy administered in combination with low dose radiation. A second infusion of MAGE-A4$^{c1032}$T cells may only be given to eligible subjects following a confirmed response (CR or PR) or clinical benefit ≥ 6 weeks after the first T-cell infusion and whose tumor continues to express the appropriate antigen target.

- Screening Protocol (ADP-0000-001): Subjects may be screened in the Screening Protocol for the presence of HLA-A*02 and for MAGE-A4 expression on the tumor (Section 7.2). The absence of HLA-A*02:05 in either allele; or the presence of HLA-A*02:07 or any A*02 null allele (designated with an "N", eg, A*02:32N) as the sole HLA-A*02 allele will also be assessed as these are study exclusion criteria.
- Screening and Interventional Phase (ADP-0044-001): Subjects with the relevant HLA alleles and MAGE-A4 tumor antigen will sign the study Informed Consent Form (ICF) and enter the Screening Phase in this protocol to determine eligibility for the Interventional Phase of the study. If the subject meets the study eligibility criteria (Section 4), the subject begins the Interventional Phase of the study which runs until disease progression, death, or withdrawal. Subjects that have Progressive Disease (PD) or withdrawal prior to 3 months 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 3 months post infusion (see Section 4.3). During the period in which the subject is being considered for a second infusion they will remain in the Interventional Phase.
- Long Term Follow-up Phase (ADP-0044-001): Subjects who end the interventional phase, will continue in the Long Term Follow-Up (LTFU) Phase of the study to continue long term monitoring for potential gene therapy-related delayed adverse events for 15 years post infusion (Section 7.4.9). 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.

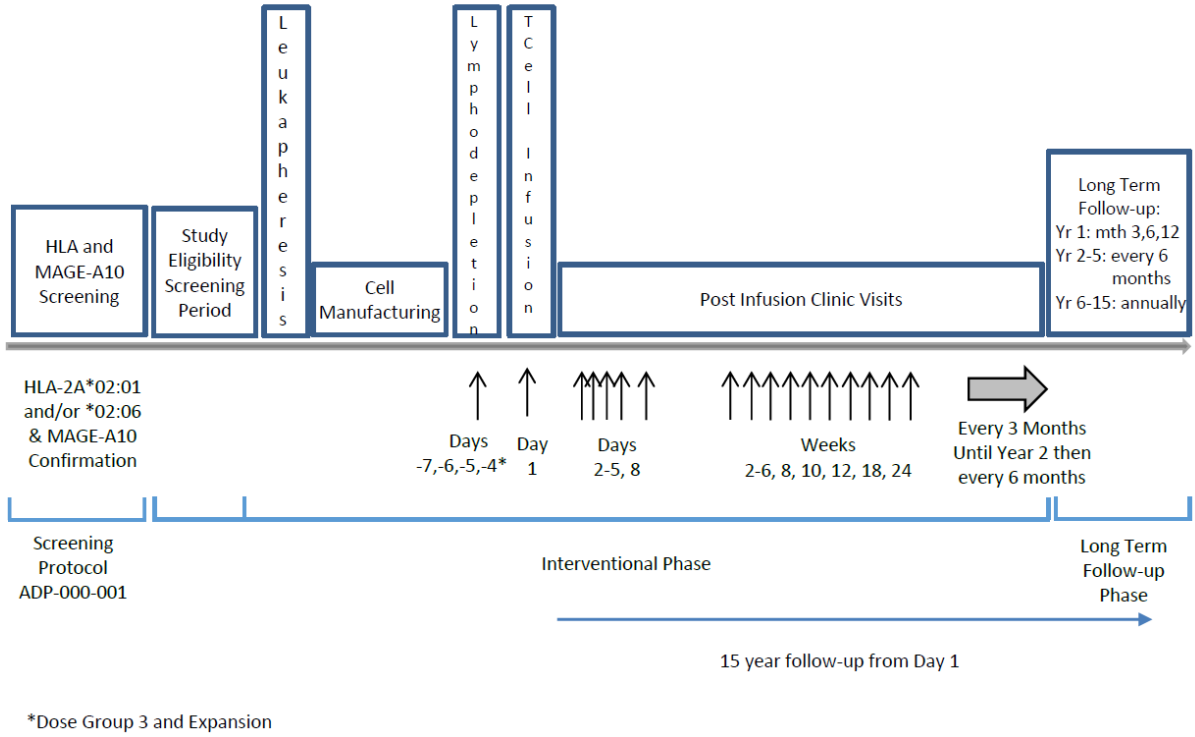
Leukapheresis is performed to obtain cells for the manufacture of autologous MAGE-A4$^{c1032}$ TCR bearing T cells. Leukapheresis should be performed as soon as feasible after the subject is determined to be eligible for study participation and may be performed prior to disease progression in subjects undergoing treatment for locally advanced or metastatic disease at the discretion of the investigator.

Prior to the administration of lymphodepleting chemotherapy eligibility criteria as noted in Section 4.1 and Section 4.2 will be reconfirmed and Baseline tumor assessment obtained. When the MAGE-A4$^{c1032}$T cells are manufactured and available at the investigational site, subjects will undergo lymphodepleting chemotherapy with cyclophosphamide and fludarabine (Section 5.2) followed by infusion of MAGE-A4$^{c1032}$T (Section 5.3.2) on Day 1. Granulocyte colony-stimulating factor (G-CSF) support should start on Day 3 after T cell infusion and be given until resolution of neutropenia in accordance with ASCO guidelines or institutional practice. The lymphodepletion may be given as an outpatient procedure. The T cell infusion should be given as an inpatient procedure. All subjects enrolled during the dose escalation phase of the study who are infused with MAGE-A4$^{c1032}$T cells should be admitted to the hospital for observation of potential toxicities including on-target, off-tumor toxicities, for at least 72 hours and may be discharged if medically stable at the discretion of the investigator. Subjects will be followed daily for the first week post- infusion on Days 2-5 and Day 8. Subjects may be hospitalized for follow-up care at the discretion of the Investigator.

Safety and tolerability, including determination of dose limiting toxicity as well as anti-tumor activity and biomarker assessments to be conducted at each visit are outlined in the Schedule of Procedures (Section 7.1). Anti-tumor activity will be assessed using RECIST v1.1 criteria. To allow time for the immune response to become apparent and for potential transient inflammatory reaction of the disease to the treatment (‘tumor flare’), anti-tumor activity will not be assessed before 6 weeks post infusion of MAGE-A4$^{c1032}$T, unless there is unequivocal clinical evidence of deterioration.

In accordance with FDA and EMA follow up requirements [FDA, 2006b; EMA, 2009] for gene therapy clinical trials, long term monitoring of subjects for gene therapy related delayed AEs (LTFU) continues after the subject has progression of disease. During the first year post T cell infusion subjects will be seen in the clinic at 3, 6 and 12 months. From year 2 to 5, subjects will be seen in the clinic every 6 months. After 5 years, the subjects will be followed up annually for up to 15 years. All subjects will continue to be followed for OS during the LTFU phase.

**Figure 1: Schematic for Study ADP-0044-001**




## 3.2. Components of Study Design

### 3.2.1. Screening for HLA and MAGE-A4 (ADP-0000-001)

MAGE-A4$^{c1032}$T specifically recognizes the HLA-A*02-restricted MAGE-A4 peptide antigen HLA-A*02- GVYDGREHTV; therefore, this protocol will select for subjects with HLA-A*02 allelic variants and whose tumor expresses the MAGE-A4 antigen. Subjects must not have HLA-A*02:05 in either allele as this may be alloreactive. Subjects with either HLA-A*02:07 or any A*02 null allele (designated with an "N", eg, A*02:32N) as the sole HLA-A*02 allele (eg, a subject with HLA alleles A*02:04 and A*02:07 is eligible) are excluded as these alleles are inactive. The Sponsor will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate patient eligibility based on HLA results.

The prevalence of HLA subtypes varies from population to population. Information on the prevalence of HLA-A2 allelic variants in specific populations is available in the Allele Frequency Net Database [http://www.allelefrequencies.netIt is recommended that investigators review the database for HLA-A2 allelic variants relevant to the subject population at their site.

### 3.2.2. T cell Manufacturing

MAGE-A4$^{c1032}$T is autologous CD4 and CD8 T cells engineered with an affinity-enhanced TCR to target the tumor antigen MAGE-A4. Autologous T cells are obtained from eligible subjects who have MAGE-A4 positive tumors and who have appropriate HLA-A. The CD4 and CD8 T cells are transduced with a SIN lentivirus vector expressing the MAGE-A4 (affinity enhanced clone 1032) under GMP conditions. The product of this transduction is polyclonal T cells which are designed to target MAGE-A4 in tissue. The transfer SIN lentiviral vector has been meticulously designed to contain only the minimal genetic elements required for function and no vector proteins for maximum biosafety [Dull, 1998]. Many reports provide evidence supporting the relative biosafety of SIN lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the lentivirus long terminal repeat (LTR) in comparison to the γ retroviral vectors [Montini, 2006; Maruggi, 2009; Modlich, 2009; Montini, 2009].

Cell product typically is ready to be returned to the investigational site approximately 1 month after subject apheresis. Any unused or leftover patient leukapheresis material may be used by the Sponsor for performing additional research studies to modify or improve the manufacturing process and to enhance the clinical response. Additional details are provided in the MAGE-A4$^{c1032}$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 lymphocytes [Baccala, 2005] and facilitate trafficking of the engineered T cells [Pinthus, 2004]. Lymphodepletion also enhances the activity of the adoptively transferred cells via the removal of inhibitory factors such as regulatory T cells [Wolf, 2003] and can activate antigen presenting cells through the induction of inflammatory cytokines and induction of tumor apoptosis with resulting cross presentation of tumor antigens to T cells.

Recent evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia and acute leukemia using adoptive cellular therapy including a CAR showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in a previously cyclophosphamide-only preparative regimen [Turtle, 2015]. Based on the results from previous clinical research using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy and the increasing evidence that fludarabine is a key component, the lymphodepleting regimens in this study consist of intravenous fludarabine 30 mg/m$^2$/day for 3 days (Day -7 to Day -5) and cyclophosphamide 600 mg/ m$^2$/day for 3 days (Days -7 to -5) in dose Groups 1 and 2, fludarabine 30 mg/m$^2$/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m$^2$/day for 3 days (Days -7 to -5) in dose Group 3, the Expansion Group and in the substudy population.

### 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-A4 (see Section 5.3.2 for administration details).

### 3.2.5. Rationale for MAGE-A4$^{c1032}$T Dose Escalation

Activity seems to be indirectly related to dose administered, potency, cell expansion and persistence. High T cell doses may be associated with an increased risk of AEs. Total T cell doses up to approximately 100 × $10^9$ cells of NY-ESO TCR [Robbins, 2011] have been used although the actual potency of the products may differ depending on manufacturing methods. Conversely, doses as low as 0.015 × $10^9$ (15 million) cells may also be effective in other adoptive cell transfer settings such as CAR T cells [Porter, 2011].

Our current experience with another TCR product, NY-ESO-1$^{c259}$T, is with total cell doses in the range of approximately <1 to 15 × $10^9$ transduced cells with a transduction level of approximately 18% to 78%, where long term persistence and anti-tumor responses have been observed in 50% of subjects.

The initial dose selected for MAGE-A4$^{c1032}$T is 0.1 × $10^9$ transduced cells to be escalated to 1 × $10^9$ and then to 5 × $10^9$ transduced cells in a modified 3 + 3 dose escalation scheme (Table 1). 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 30 subjects in the Expansion Group and up to 10 additional subjects in the sub study population). This dose range falls within the overall range that has been effective and safe in NY-ESO-1$^{c259}$T clinical trials to date. As with NY-ESO-1 $^{c259}$T, MAGE-A4$^{c1032}$T will be administered by a single intravenous (IV) infusion.

**Table 1: Cell Dose Groups**

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

[1] For subjects in all cell dose groups whose cells fail to meet the cell dose requirement during the manufacturing process, re-leukapheresis and/or re-manufacturing may be requested.

[2] If in any Group, 1 out of 3 subjects experiences a DLT requiring expansion of an additional 3 subjects (n=6), the observation period will be increased from 7 days to 14 days for the 3 subsequent treated subjects

[3] If Group 3 is selected as the optimal dose group and expanded to 30 subjects, the maximum dose range will be increased to 10 x $10^9$ transduced cells for the subjects in the expansion cohort (ie. after 3-6 subjects are treated in the dose escalation stage) and for subjects in the stubstudy population.
[4] Group 3 will be treated with Cyclophosphamide 600mg/$m^2$/day on Days -7, -6, -5 and fludarabine 30 mg/$m^2$/day on Days -7, -6, -5 and -4 as described in Table 4.

In Group 1, initiation of lymphodepleting chemotherapy in the first 3 subjects will be staggered: lymphodepletion of a subject will occur only after the previous subject has completed a minimum observation period of 21 days from T cell infusion. If there are no DLTs in the first 3 subjects treated in Group 1, then lymphodepletion can proceed into the next higher dose (Groups 2 and 3) with a 7-day observation period between subjects. 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.

**Decision Making Guidelines for Dose Escalation**

*(Based on number of subjects developing a DLT)*

- A) 0 out of 3 subjects; escalate to next cell dose level
- B) 1 out of 3 subjects; enroll 3 additional subjects at current cell dose level
    - B1) 1 out of 6 subjects; escalate to next cell dose level
    - B2) 2 out of 6 subjects; halt dose escalation and potentially declare previous dose as Maximum Tolerated Dose (MTD) (if these DLTs were observed in Groups 2 or 3), OR Safety Review Committee (SRC, see Section 10.1) may recommend to add 3 additional subjects at this dose level for a total of 9 subjects to further characterize toxicity following review by FDA.
        - If DLT rate remains 2 out 9, the SRC may recommend escalating to next group.
        - A 3rd DLT during cohort expansion to N=9 would result in pausing of dose escalation and the previous dose may be declared the MTD.
    - B3) >2 out of 6 subjects would result in pausing of dose escalation; MTD may be declared to be the previous dose.
- C) 2 out of 3 subjects; halt dose escalation and potentially declare previous dose as MTD (if these DLTs were observed in Groups 2 or 3), OR SRC (see Section 10.1) may recommend to add 3 additional subjects at this dose level for a total of 6 subjects following review by FDA. If no further DLTs are observed (i.e. 2 out of 6 DLT), SRC will review the data and may recommend to add 3 additional subjects at this dose level for a total of 9 subjects to further characterize toxicity following review by FDA. If DLT rate remains 2 out 9, the SRC may recommend escalating to next group.
- D) 3 out of 3 subjects; dose escalation is halted and MTD is the previous dose (if these DLTs were observed in Groups 2 or 3).

After initiation of the expansion phase (see Section 3.2.6) at the highest tolerated dose, DLTs will continue to be monitored. If at any point during this expansion the predictive probability that the DLT rate exceeds 33% with 30 subjects (end of expansion) is greater than or equal to 50%, the SRC will evaluate the totality of the MAGE-A4 safety data to date to determine whether enrollment should be paused or whether additional risk management steps are required (see Section 11.2).

### 3.2.6. Number of Subjects Adjustments

This is a modified 3 + 3 dose escalation trial with up to 3 dose groups. The sample size of each group is anticipated to be between 3 and 6 subjects, for a total of up to 18 subjects treated during dose escalation. As described above, a group may be expanded to N=9 after SRC and FDA review of 2 DLTs in 6 subjects. The target cell dose range may be expanded up to approximately 30 subjects (inclusive of the subjects treated in the cell dose escalation phase) to characterize safety. Up to an additional 10 subjects will be treated with the target cell dose range in the ADP-0044-001R substudy. The overall sample size of the study inclusive of the expansion phase and the substudy is estimated to be approximately 52 treated subjects (as described in Section 3.4).

## 3.3. Evaluation of Dose-Limiting Toxicity and Study Stopping Rules

### 3.3.1. Dose Limiting Toxicity

Each cell dose group in the escalation phase will treat a minimum of 3 subjects unless precluded by DLT in the first 2 subjects. In this case, enrolment will be paused until safety evaluation is performed. Toxicity assessment in treated subjects, 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 version 4.0), regardless of the Investigator's assessment of relationship to the gene-modified T cell infusion

Unlike other medicinal products where dose or pharmacokinetic exposure correlates with toxicity, the correlation between cell dose and toxicity is not as clearly defined with T cell therapies. Expansion of the cells after infusion may play a role in both toxicity as well as anti-tumor activity. DLTs and MTD are terms typically used in dose escalating study designs of "non-living" compounds with more predictable pharmacokinetic properties. In this study, these terms are used to refer to toxicities that reach a level of severity that would warrant careful evaluation.

**NOTE:** The DLT observation period will be during the first 30 days following the infusion of MAGE-A4$^{c1032}$T for each subject in all groups, and will therefore exclude the time interval between conditioning and cell infusion. In evaluating potential DLTs, there may be a toxicity considered attributable to the disease or lymphodepleting chemotherapy regimen. For toxicities considered clearly attributable to the underlying malignancy, chemotherapy, or otherwise clearly

unrelated to the T-cell product the SRC may assess that the toxicity is not deemed a DLT. Two DLTs in one group will not automatically result in determination of a MTD. For these events, the independent 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 10.1 for details of the SRC.

While the observation period for DLTs is 30 days post infusion, Grade ≥3 toxicities that occur more than 30 days following T cell infusion may be also considered DLTs by the Investigator after consultation with the Sponsor. Events determined to be DLTs will be reported to the regulatory authorities if appropriate, in accordance with the standards for expedited reporting.

The following toxicities are NOT considered DLTs:

- Grade 3 or 4 fever resolving to grade 2 or below within 72 hours
- Grade 3 or 4 febrile neutropenia resolving to Grade ≤ 2 within 14 days
- Grade 3 anemia
- Grade 3 or 4 leukopenia or neutropenia resolving to Grade ≤ 2 within 28 days
- Grade 3 or 4 lymphopenia
- Grade 3 or 4 thrombocytopenia not associated with significant bleeding; Grade 4 thrombocytopenia must resolve to ≥25 x $10^9$/L within 14 days
- Grade 3 colitis resolving to Grade ≤2 within 7 days
- Grade 3 diarrhea, nausea or vomiting resolving to Grade ≤2 with supportive treatment within 3 days after onset
- Grade 3 or 4 CRS, or toxicities related to CRS, resolving to Grade ≤2 within 7 days
- Grade 3 rash resolving to Grade ≤2 within 7 days
- Grade 3 or 4 hypoalbuminemia or abnormal electrolytes responding to supplementation/correction
- Grade 3 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation resolving to Grade ≤2 or Baseline within 7 days
- Grade 3 generalized weakness or fatigue not resolved to Grade ≤2 within 7 days

### 3.3.2. Early Stopping Rules

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 the Sponsor in collaboration with a SRC (refer to Section 10.1 for details of the SRC). Based on the severity of the DLTs, the degree of T cell expansion, indicators of potential anti-tumor activity, and other factors, a recommendation whether to halt the study; modify the study (i.e. enroll additional subjects to further characterize safety at a given cell dose); or continue enrollment will be made

collaboratively with input from the SRC, the Sponsor, and Investigators. Final decisions to halt or modify the study will be made by Adaptimmune's Safety Governance Board.

If the following events occur, further enrolment to the study will be suspended and the regulatory authorities informed:

- Any death occurs that is deemed to be at least probably related to the MAGE-A4$^{c1032}$T cell product by the principal Investigator and study Sponsor; or
- Two or more Grade 4 autoimmune events deemed probably or definitely related to the MAGE-A4$^{c1032}$T cell product by the principal Investigator and study Sponsor; or
- A subject has a positive RCL:
  - Confirmed positive peripheral blood mononuclear cell (PBMC) RCL and no other vector lot is available (refer to Section 10.2 on monitoring and management of RCL)
  - Confirmed biological RCL - all MAGE-A4$^{c1032}$T cell infusions are halted (see Section 10.2)

Following assessment by Adaptimmune's Safety Governance Board, enrollment and dosing may resume if agreed upon by the Sponsor, SRC, and Investigators. Regulatory authorities will be notified of any decisions to halt the study or subject enrolment. The study will not enroll further subjects until the regulatory authorities have reviewed the data leading to such a decision and agree with a proposal to resume enrollment.

## 3.4. Number of Subjects and Study Duration

Subjects with inoperable or metastatic (advanced) cancers of the following types will be enrolled: urothelial, melanoma, head and neck (squamous cell), ovarian, NSCLC (squamous, adenosquamous, adenocarcinoma, or large cell), esophageal (squamous and adenocarcinoma), gastric, synovial sarcoma or MRCLS. The study will treat up to 18 subjects in the dose escalation portion using a modified 3 + 3 cell dose escalation design to evaluate DLTs and determine the target cell dose range.

Following the dose escalation phase additional subjects will be treated for a total of approximately 30 additional subjects across all the eligible tumor types, and inclusive of subjects treated at the target cell dose, to better assess overall safety and anti-tumor activity. The decision to expand treatment will be based on clinical judgment on safety, tolerability and emerging responses. Approximately 52 subjects are expected to be treated over the course of this study. 10 of the 52 subjects will be treated at the target cell dose in the ADP-0044-01R substudy.

If a subject has been enrolled to the study and undergone leukapheresis, then they may be permitted to receive the T-cell infusion even if 52 subjects have been treated, provided the benefit-risk assessment is thought to be favorable. This would require sponsor approval.

Study enrollment is expected to continue for approximately 24 months. The study will be considered completed once the last subject has been followed for 15 years from time of last T cell infusion or discontinued the study for any reason.

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

## 3.5. Sites

The protocol will be conducted in approximately 10 sites in the U.S. and Canada, inclusive of one site participating in the sub study. Additional sites may be added at the discretion of the Sponsor, including sites in EU.

## 3.6. Benefit: Risk Assessment

The results of nonclinical and planned clinical studies conducted with MAGE-A4$^{c1032}$T are summarized in the Investigator's Brochure. This section outlines the potential benefits, risks and the mitigation strategies for this study.

### 3.6.1. Benefit Assessment

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

The efficacy of MAGE-A4$^{c1032}$T has not been evaluated as of yet. Efficacy however, has been demonstrated with other ACTs, including NY-ESO-1$^{c259}$T. This supports the potential therapeutic benefit of TCR therapy in subjects with malignancies expressing the relevant antigen.

NY-ESO-1$^{c259}$T was the first Adaptimmune TCR to be studied in subjects with cancer. At least 69 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 [Rapoport, 2015], synovial sarcoma [D'Angelo 2017], melanoma, MRCLS [D'Angelo 2018b] and melanoma (NCT01350401). Additionally, 38 subjects were treated in an Investigator sponsored study conducted by the NCI [Robbins, 2008; Zhao, 2007], where the T cells were modified using a retroviral vector, expanded using NCI cell processing methods and administered in conjunction with IL-2. 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; Merchant, 2015]. 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 nCR or CR and 32% had PRs [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 PR). Median duration of response was more than 6 months [Merchant, 2015]. 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-A4$^{c1032}$T which has incorporated learnings from other adoptive T cell therapy programs (MAGE-A4$^{c1032}$T Investigator Brochure); (2) based on the preclinical alloreactivity data, exclusion of subjects with HLA-A*02:05 in either allele or with either HLA-A*02:07 or any A*02 null allele (designated with an "N", eg, A*02:32N) as the sole HLA-A*02 allele; (3) a validated clinical trial assay with precision and reproducibility for the selection of subjects with MAGE-A4 expression in their tumors; (4) step-wise escalation of the T cell dose; (5) staggered enrollment in the first group such that there is a 21-day observation period after T cell infusion between enrollment of subjects; (6) treatment in specialized academic centers experienced with the management of toxicities associated with autologous T cell therapies; (7) guidelines for management of toxicities including CRS, GVHD, and pancytopenia/aplastic anemia as well as preventive measures for infectious complications and (8) an SRC 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-A4$^{c1032}$T. Most of these toxicities are also observed with standard of care chemotherapies or with checkpoint inhibitors. CRS, encephalopathy syndrome (ES) and pancytopenia/aplastic anemia are observed with ACTs and not typically observed with the current standard of care therapies. Guidelines for management of these toxicities are included in the protocol (Section 8). The ACTs are generally administered once. An advantage of this modality of therapy is that the vast majority of toxicities resolve within 4 to 6 weeks after T cell infusion.

### 3.6.3. Overall Benefit:Risk Conclusion

Subjects with inoperable or metastatic urothelial cancer, melanoma, head and neck cancer, ovarian cancer, advanced NSCLC (Stage IIIB or IV), esophageal cancer, gastric cancer, synovial sarcoma or MRCLS 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-A4$^{c1032}$T cells. The clinical study has taken measures to ensure safe administration of the MAGE-A4$^{c1032}$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-A4$^{c1032}$T in the clinic in the defined study population.

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

Subjects will be assessed for eligibility prior to leukapheresis AND prior to lymphodepleting chemotherapy (unless otherwise noted) and must meet all specified criteria for study participation.

## 4.1. Inclusion Criteria

A subject must meet the following inclusion criteria to be eligible for participation in this study:

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 and long term follow-up.
3. Subject is ≥18-≤75 years of age at the time of signing the study informed consent.
4. Subject has histologically confirmed diagnosis of any one of the following cancers: (A) urothelial cancer (transitional cell cancer of the bladder, ureter, urethra or renal pelvis), (B) melanoma, (C) squamous cell carcinoma of the head and neck, (D) ovarian cancer, (E) NSCLC (squamous, adenosquamous, adenocarcinoma, or large cell), (F) esophageal (squamous and adenocarcinoma) or (G) gastric cancer, (H) synovial sarcoma or (I) MRCLS.
5. Subject has measurable disease according to RECIST v1.1 criteria prior to lymphodepletion. Measurable disease is not required prior to leukapheresis.
6. Subject has the following disease specific requirements for their tumor type (Note: there is no limit to the number of therapies prior to study entry):
    - Inoperable or metastatic (advanced) urothelial cancer

      Has received at least one prior systemic therapy in the adjuvant or metastatic setting; may have received treatment with a PD-1/PD-L1 inhibitor.
    - Inoperable or metastatic (advanced) melanoma
        - Has received, is intolerant, or refused a CTLA-4 inhibitor (ipilimumab) or a PD-1 inhibitor (nivolumab or pembrolizumab) as monotherapy or a combination of ipilumumab and nivolumab.
        - Has received or is intolerant of a BRAF inhibitor or the combination of BRAF and MEK inhibitors for BRAFv600 mutant melanoma.
    - Inoperable or metastatic (advanced) squamous cell head and neck cancer

  - Has received a platinum containing chemotherapy for treatment of primary tumor in adjuvant, locally advanced, or metastatic settings, is intolerant, or refused such treatment. May have received prior immunotherapy.

- Inoperable or metastatic (advanced) ovarian, primary peritoneal or fallopian tube carcinoma
  - Has received platinum containing chemotherapy and has platinum refractory or resistant disease.
  - If platinum sensitive disease, should have received ≥2 lines of chemotherapy.
  - May have received PARP inhibitors, bevacizumab, or immunotherapy.
- Histologically or cytologically confirmed diagnosis of advanced NSCLC (Stage IIIB or IV) or recurrent disease
  - Has squamous cell, adenosquamous, adenocarcinoma or large cell carcinoma.
  - Has received at least one prior systemic therapy.
  - Subjects whose tumors are known to have EGFR mutations or ALK gene rearrangements must have failed (progressive disease or unacceptable toxicity) prior EGFR inhibitor or ALK tyrosine kinase inhibitor, respectively.
  - Subjects with ROS-1 positive tumors must have failed an ALK inhibitor (crizotinib).
  - May have received PD-1 inhibitors.
- Inoperable or metastatic (advanced) squamous or adenocarcinoma of the esophagus, gastro-esophageal junction or gastric cancer
  - Has received, is intolerant, or refused at least one 5-FU and/or platinum containing regimen.
  - Subjects whose tumors are known to have Her2neu amplification must have failed (progressive disease or unacceptable toxicity) or refused trastuzumab.
  - May have received ramucirumab.
- Subject has a diagnosis of advanced (metastatic or inoperable) synovial sarcoma or high grade myxoid liposarcoma / myxoid round cell liposarcoma confirmed by histology or cytogenetics.
  - Subjects with synovial sarcoma must have previously received an anthracycline containing regimen. Subjects who are intolerant to anthracycline may have received ifosfamide alone.
  - Subjects with MRCLS must have previously received or be intolerant to an anthracycline containing regimen.

7. Subject is HLA-A*02 positive. (This determination will be made under Screening protocol ADP-0000-001). The Sponsor 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) shows expression of the MAGE-A4 RNA or protein. All samples must have been reviewed by an Adaptimmune designated central laboratory confirming expression. (This determination will be made under Screening Protocol ADP-0000-001).
9. Subject has anticipated life expectancy > 6 months prior to leukapheresis and >3 months prior to lymphodepletion.
10. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1.
11. Subject has a left ventricular ejection fraction ≥50%.
12. Subject is fit for leukapheresis and has adequate venous access for the cell collection.
13. Female subject of childbearing potential (FCBP) must have a negative urine or serum pregnancy test. NOTE: FCBP is defined as premenopausal and not surgically sterilized. FCBP must agree to use maximally effective birth control or to abstain from heterosexual activity throughout the study, starting at the first dose of chemotherapy for 12 months after receiving the investigational product, or 4 months after there is no evidence of persistence/gene modified cells in the subject's blood, whichever is longer.

    OR

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

**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 |
| Hemoglobin | >80 g/L (without transfusion support within 7 days prior to leukapheresis) |
| **Coagulation** | |
| Prothrombin time (PT) or International Normalized Ratio (INR) | ≤1.5 × upper limit of normal (ULN) unless receiving therapeutic anticoagulation. |

| | |
|---|---|
| Partial thromboplastin time (PTT) | ≤1.5 × ULN unless receiving therapeutic anticoagulation. |
| **Renal** | |
| Calculated or measured creatinine clearance [1] | ≥ 60 mL/min<br>Exception: subjects with urothelial or ovarian cancer ≥40 mL/min |
| **Hepatic** | |
| Serum total bilirubin | ≤1.5 × ULN (unless subject had documented Gilbert's Syndrome) |
| Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT) | ≤2.5× 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 EDTA GFR measurement, according to standard practice at the treating institution.

Renal function will be reassessed at Baseline.

## 4.2. Exclusion Criteria

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

1. HLA-A genotype (The sponsor will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate patient eligibility based on HLA results):
   - Subject is HLA-A*02:05 positive in either allele.
   - Subject has HLA-A*02:07 as the sole HLA-A*02 allele (eg, a subject with HLA alleles A*02:04 and A*02:07 is eligible).
   - Subject has any A*02 null allele (designated with an "N", eg, A*02:32N) as the sole HLA-A*02 allele.
2. Subject has received or plans to receive the following excluded therapy/treatment: prior to leukapheresis or lymphodepleting chemotherapy:

| Treatment/Therapy | Required Wash-out Prior to Leukapheresis | Required Wash-out Prior to Lymphodepletion |
|---|---|---|
| Cytotoxic chemotherapy | 3 weeks | 3 weeks |
| Small Molecules/Tyrosine kinase inhibitor (TKI) such as dabrafenib, trametinib, vemurafaneb and cobimetinib. NOTE: No washout period is required for compounds that do not cause bone marrow suppression/lymphopenia or for EGFR and ALK/ROS-1 inhibitors unless the multi-kinase inhibitor targets VEGFR (e.g. afatinib), PDGFR or c-Kit receptors | 1 week | 1 week |
| Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors, biologics) | 2 weeks | 2 weeks |
| Experimental anti-cancer Vaccine | N/A | 2 months in the absence of tumor response.<br>The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months |
| Gene therapy using an integrating vector | Any use of previous gene therapy using an integrating vector is not permitted | Any use of previous gene therapy using an integrating vector is not permitted |
| Corticosteroids or any other immunosuppressive therapy. NOTE: Use of topical steroids and inhaled steroids are not an exclusion. See Section 6.1 for exceptions. | 2 weeks | 2 weeks |
| Investigational treatment | 2 weeks or 5 half-lives, whichever is shorter | 2 weeks or 5 half-lives, whichever is shorter |
| Radiotherapy that involves the lung (V20 exceeding 30% lung volume) or pericardium (>20Gy). NOTE: Exception for a lesser dose or 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. | N/A | 3 months |
| Radiation to vital organs (e.g. liver, kidney) | N/A | 4 weeks |
| Radiation to the pelvis | 4 weeks | 4 weeks |
| Whole Brain Radiotherapy (WBRT) or Brain Stereotactic Radiosurgery (SRS) | N/A | 2 weeks |

| Treatment/Therapy | Required Wash-out Prior to Leukapheresis | Required Wash-out Prior to Lymphodepletion |
|---|---|---|
| Radiotherapy to the target lesions | N/A | 3 months prior to lymphodepleting chemotherapy. A lesion with unequivocal progression may be considered a target lesion. (Note: there is no washout period for palliative radiation to non-target organs). |
| NOTE: Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician | | |

3. Subject that has toxicity from previous anti-cancer therapy must have recovered to ≤Grade 1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible e.g. peripheral neuropathy) can be enrolled.
4. Subject has history of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study.
5. Subject has history of chronic or recurrent (within the last year prior to Screening) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments, including anti-TNF agents.
6. Subject had major surgery within 4 weeks prior to lymphodepletion; subjects should have been fully recovered from any surgical related toxicities.
7. Subject has symptomatic CNS metastases. Subject with a prior history of symptomatic CNS metastases must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiation (WBRT) or surgery) and be neurologically stable for at least 1 month, not requiring anti-seizure medications and off steroids for at least 14 days prior to leukapheresis and lymphodepletion. Subject who has asymptomatic CNS metastatic disease without associated edema, shift, requirement for steroids or anti-seizure medications are eligible. If such a subject receives SRS or WBRT, a minimum period of 2 weeks needs to lapse between the therapy and lymphodepletion. Subjects with leptomeningeal disease or carcinomatous meningitis are NOT eligible.
8. Subject has any other active malignancy besides the tumor under study within 3 years prior to Screening. Exceptions: adequately-treated malignancies not likely to require therapy (e.g., completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma). Newly identified prostate cancers found during cytoprostatectomy are permitted. Subjects must be in complete remission from prior malignancy in order to be eligible to enter the study.
9. Subject has an electrocardiogram (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 [BBB]) over 3 consecutive ECGs. Either Fridericia's or Bazett's formula may be used to correct the QT interval.

10. Subject has uncontrolled intercurrent illness including, but not limited to:
    - Ongoing or active infection.
    - Clinically significant cardiac disease defined by CHF New York Heart Association (NYHA) >Class1; uncontrolled clinically significant arrhythmia in last 6 months; acute coronary syndrome (ACS) (angina or myocardial infarction) in last 6 months.
    - Interstitial lung disease (pneumonitis), history of pneumonectomy, or of COPD with ≥ one exacerbation within 1 year prior to the Screening visit that required treatment with systemic corticosteroids or resulted in hospitalization.
    - 
    - Pre-existing active skin disorders of Grade 2 or greater severity.
    - 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
11. Subjects who in the opinion of the Investigator will be unlikely to fully comply with protocol requirements.
12. Subject has active infection with HIV, HBV, HCV or HTLV as defined below:
    - Positive serology for HIV.
    - Positive HBV surface antigen test. Positive HBV DNA test. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months (see Section 8.2.4).
    - Positive hepatitis C RNA test. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value
    - Positive serology for HTLV 1 or 2.

    Re-screening for infectious disease markers is not required at Baseline (prior to lymphodepletion).
13. Subject is pregnant or breastfeeding.

## 4.3. 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 4.1 and Section 4.2 and meet the following inclusion criteria:

1. Subject has had a documented confirmed response (PR or CR) or clinical benefit ≥ 6 weeks after the first T-cell infusion and then progress.
2. A second T cell infusion is recommended by the Investigator.
3. Subject has a new tumor biopsy confirming MAGE-A4 expression.
4. Subject has voluntarily agreed to receive a second T-cell infusion by giving written informed consent.
5. Any toxicities from first T cell infusion have 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 to collect cells for new product manufacture.

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

- Subject with any Grade 4 CRS or clinically life-threatening (Grade 4) AEs deemed at least possibly related to the MAGE-A4$^{c1032}$T cell product by the Investigator and study Sponsor reported during the first T-cell infusion.

Subjects must receive the second infusion within 6 months of progression following their first infusion.

## 4.4. 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 progression of disease (see Section 7.4.8 for tumor response assessments), has died before progressing, or is withdrawn. Subjects that have PD or withdraw prior to 3 months 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 3 months post infusion. Subjects being considered for eligibility for second infusion may remain in the Interventional Phase for up to 6 months after progression prior to a second infusion. They will enter the LTFU phase after they are deemed ineligible for second infusion or when they end the Interventional Phase after the second infusion. 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 [FDA, 2006b; EMA, 2009]. 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. . This study will be considered complete when the last subject has discontinued from the study for any reason.

## 4.5. 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. 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'.

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

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

### 4.5.1. Ending the Interventional Phase

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

- 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 7.4.9 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.

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.

### 4.5.2. Discontinuation from the study

Reasons for discontinuation of a subject from the study may 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.

# 5. STUDY TREATMENTS

## 5.1. Leukapheresis

Subjects who complete screening procedures defined in the Screening Protocol ADP-0000-001 and Section 7.2 and who meet eligibility criteria as defined in Section 4 will be eligible to undergo leukapheresis to obtain starting material for the manufacture of autologous MAGE-A4$^{c1032}$T cells. Prior to leukapheresis, an absolute lymphocyte count of ≥0.5 x $10^9$/L and the CD3 count ≥200/µL is recommended if locally available.

For collection of starting material a large-volume non-mobilized PBMC collection should be performed according to institutional standard procedures. Two to three blood volumes should be processed with a goal of collecting 1.0 × $10^8$ PBMC/kg body weight and a minimum of 1.5 × $10^7$ PBMC/kg. In cases where the minimum number of PBMC is not collected or the T cells are not able to be infused back to the subject, a second leukapheresis may be performed. Citrate anticoagulant should be used. Prophylactic 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-A4$^{c1032}$T cell product has been manufactured, has met release criteria, and has arrived at the clinical site, eligible subjects will proceed to have lymphodepleting chemotherapy followed by infusion of the MAGE-A4$^{c1032}$T cell product as detailed in Section 5.2 and Section 5.3.2, respectively.

## 5.2. Lymphodepleting Chemotherapy

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

When the MAGE-A4$^{c1032}$T cells have completed manufacture, have fulfilled release criteria, and the product has been received at the investigational site, fludarabine and cyclophosphamide will be used as lymphodepleting chemotherapy prior to administration of the investigational product (IP) as described in Table 3.

Appropriate intravenous (IV) hydration should be administered and Mesna should be given to prevent urotoxicity while cyclophosphamide is administered, as described below. Other premedication (e.g. anti-emetics) may also be provided in accordance with institutional standards. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. G-CSF should be given to all subjects starting on Day 3 until resolution of neutropenia in accordance with ASCO guidelines or institutional practice (see Section 8.9.1).

On admission for lymphodepleting chemotherapy subjects should commence antimicrobial and antifungal prophylaxis in line with institutional standard practice (see Section 8.2).

## Table 3: Fludarabine and Cyclophosphamide Treatment Schema: Dose Group 1 & 2

| Lymphodepleting Chemotherapy Groups 1 and 2 | | | | | Recommended Prophylaxis and Supportive Medication |
|---|---|---|---|---|---|
| **Day** | **Drug** | **Dose** | **Route** | **Administration** | **Infection:** On admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis (see Section 8.2), or in line with institutional guidelines.<br>**Hydration:** Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions<br>**Mesna:** May be given to prevent urotoxicity per institutional guidelines or as recommended in Section 5.2.2<br>**G-CSF:** Recommended starting 24 hours after the last cyclophosphamide infusion until resolution of neutropenia in accordance with ASCO guidelines or institutional guidelines (Section 8.9.1)[1]<br>**Cell therapy premedication:** Premedication with acetaminophen and diphenhydramine should be given approximately 30 minutes prior to the infusion according to institutional guidelines. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. |
| -7 | **Fludarabine**[2] | 30 mg/m$^2$ | IV | in 50-100mL 0.9% NaCl over 30 mins[3,4] | |
| | **Cyclophosphamide** | 600 mg/m$^2$ | IV | in 100-250mL 0.9% NaCl over 1 hour[4] | |
| -6 | **Fludarabine**[2] | 30 mg/m$^2$ | IV | in 50-100mL 0.9% NaCl over 30 mins[3],[4] | |
| | **Cyclophosphamide** | 600 mg/m$^2$ | IV | in 100-250mL 0.9% NaCl over 1 hour[4] | |
| -5 | **Fludarabine**[2] | 30 mg/m$^2$ | IV | in 50-100mL 0.9% NaCl over 30 mins[3],[4] | |
| | **Cyclophosphamide** | 600 mg/m$^2$ | IV | in 100-250mL 0.9% NaCl over 1 hour[4] | |
| -4 | start **G-CSF**[6] | | | | |
| -3 | | | | | |
| -2 | | | | | |
| -1 | | | | | |
| 1 | **MAGE-A4$^{c1032}$T infusion**[5] | | | | |

[1] 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
[2] Fludarabine dose will be adjusted in renal impairment as described in Section 5.2.1
[3] Concentration of 1mg/ml or less
[4] Or per institutional guidelines
[5] Administration of MAGE-A4$^{c1032}$T infusion is described in Section 5.3.
[6] Start G-CSF for dose group 1 and 2 at Day -4.

## Table 4: Fludarabine and Cyclophosphamide Treatment Schema: Dose Group 3 and Expansion

| Lymphodepleting Chemotherapy Group 3 | | | | | Recommended Prophylaxis and Supportive Medication |
|---|---|---|---|---|---|
| **Day** | **Drug** | **Dose** | **Route** | **Administration** | **Infection:** On admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis (see Section 8.2), or in line with institutional guidelines.<br>**Hydration:** Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions<br>**Mesna:** May be given to prevent urotoxicity per institutional guidelines or as recommended in Section 5.2.2<br>**G-CSF:** Recommended starting 24 hours after the last fludarabine infusion until resolution of neutropenia in accordance with ASCO guidelines or institutional guidelines (Section 8.9.1)[1]<br>**Cell therapy premedication:** Premedication with acetaminophen and diphenhydramine should be given approximately 30 minutes prior to the MAGE-A4$^{c1032}$T infusion according to institutional guidelines. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. |
| -7 | **Fludarabine**[2] | 30 mg/m$^2$ | IV | in 50-100mL 0.9% NaCl over 30 mins[3,4] | |
| | **Cyclophosphamide** | 600 mg/m$^2$ | IV | in 100-250mL 0.9% NaCl over 1 hour[4] | |
| -6 | **Fludarabine**[2] | 30 mg/m$^2$ | IV | in 50-100mL 0.9% NaCl over 30 mins[3],[4] | |
| | **Cyclophosphamide** | 600 mg/m$^2$ | IV | in 100-250mL 0.9% NaCl over 1 hour[4] | |
| -5 | **Fludarabine**[2] | 30 mg/m$^2$ | IV | in 50-100mL 0.9% NaCl over 30 mins[3],[4] | |
| | **Cyclophosphamide** | 600 mg/m$^2$ | IV | in 100-250mL 0.9% NaCl over 1 hour[4] | |
| -4 | **Fludarabine**[2] | 30 mg/m$^2$ | IV | in 50-100mL 0.9% NaCl over 30 mins[3],[4] | |
| -3 | start **G-CSF** | | | | |
| -2 | | | | | |
| -1 | | | | | |
| 1 | **MAGE-A4$^{c1032}$T infusion**[5] | | | | |

[1] 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
[2] Fludarabine dose will be adjusted in renal impairment as described in Section 5.2.1
[3] Concentration of 1mg/ml or less
[4] Or per institutional guidelines
[5] Administration of MAGE-A4$^{c1032}$T infusion is described in Section 5.3.

### 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 according to institutional practice or as recommended below:

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

## 5.3. T Cell Infusion

### 5.3.1. Premedication

Subjects will be premedicated with antihistamine and acetaminophen (paracetamol) 30 to 60 minutes prior to the T cell infusion according to institutional practice. 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 MAGE-A4$^{c1032}$T by IV 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 label is correctly matched to the subject, as per the Apheresis and T-cell Manual.

MAGE-A4$^{c1032}$T must not be thawed until immediately prior to infusion. The T-cell product should be thawed at a set temperature of 37ºC 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, 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 2-8ºC 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, as per the Apheresis and T-cell Manual.

The cell product must not be washed or otherwise processed. MAGE-A4$^{c1032}$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 to 250 mL of 0.9% sodium chloride should be connected to the second lumen of the infusion set, used to prime the line, and then the lumen closed.

On completion of the infusion of a bag of MAGE-A4$^{c1032}$T, the main line should be closed and approximately 50 mL saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided. On completion of the cell infusion the set should be flushed using additional saline from the attached bag.
In the event that Institutional practice requires a single spike infusion set (e.g. macro drip IV tubing) standard institutional guidelines for the infusion of autologous cell infusion should be followed. The line must be flushed with 0.9% sodium chloride once the infusion is complete.

In the event of adverse reaction to the cell infusion the infusion rate should be reduced, and the reaction managed according to institutional standard procedures. Steroid treatment should be avoided unless medically required. In the event a subject develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia (see Section 8).

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

Subjects who have a confirmed response (CR or PR) or clinical benefit ≥ 6 weeks after the first T-cell infusion and then progress, and whose tumors continue to express MAGE-A4, can be considered for a second infusion with MAGE-A4$^{c1032}$T. Subjects must continue to meet eligibility criteria for the study in addition to those specified in Section 4.3 prior to receiving a second infusion.

The second infusion may be given within 6 months of PD and after at least 12 weeks have elapsed from the time of previous infusion. During the period in which the subject is being considered for a second infusion they will remain in the Interventional Phase and new or changes in AEs as defined in Section 9 must be recorded in the electronic data capture (EDC) system. In addition, blood for persistence (for safety) and RCL monitoring must be collected at the time points noted in the Schedule of Procedures (Section 7.1). However, no other clinical assessments or procedures are required until the subject is screened for the second infusion. Subjects will be permitted to receive anti-cancer treatment as long as specified washout criteria are met prior to new leukapheresis or infusion.

Prior to determining eligibility for a second 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. For those subjects who will not require another leukapheresis collection of cells, please follow the clinical procedures and assessments beginning at the Baseline visit. For subjects who do require another leukapheresis, please follow the clinical procedures and assessments noted for Screening, Leukapheresis, and Baseline visits as outlined in (Section 7.1) with the exception of the following procedures, which are not required:

- Demographics
- Tumor biopsy at Baseline

**NOTE:** After the first T cell infusion, if a fresh biopsy was taken to confirm continued expression of MAGE-A4 at the time of PD and there is sufficient tumor sample remaining, this sample may be used as the Baseline sample for the Second Infusion.

These subjects will then continue to follow the clinical assessment and procedures outlined in Section 7.1 from the Lymphodepleting Chemotherapy visit onward.

Subjects that qualify for a second infusion will receive the chosen optimal lymphodepleting chemotherapy regimen and T cell infusion defined in Table 3 and Table 4.

# 6. CONCOMITANT MEDICATION AND TREATMENT

## 6.1. Prohibited concomitant medication and treatment

In the absence of disease progression, approved or investigational anticancer therapies, including non-protocol chemotherapy, immune therapy, and biological therapy (including targeted therapies with TKIs or monoclonal antibodies), are prohibited during the Interventional Phase of the study. Subjects should also not undergo other anticancer locoregional therapies such as surgical resection or non-palliative radiation. Subjects who undergo any active anticancer therapy prior to disease progression will be discontinued from the Interventional Phase and will continue in the LTFU phase.

See Section 4.2 for details of washout and excluded treatments prior to leukapheresis or lymphodepleting therapy.

The use of systemic steroids may abrogate the effects of the T cell therapy and should be avoided unless required to manage CRS (see Section 8.5 for CRS treatment recommendations) or other significant immune-mediated AEs. According to local standard of care, or ASCO guidelines, steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the IP (Day -3). Steroid use is permitted for prophylaxis or treatment of contrast dye allergies. Physiological doses of steroids, including stress doses when clinically appropriate, may be administered as replacement therapy in subjects with adrenal insufficiency. Fludrocortisone is permitted. In general, daily prednisone doses of 0.5 mg/kg or lower, or their equivalent for other corticosteroid agents are acceptable, provided that the subject continues to meet eligibility criteria (Section 4.1 and 4.2). Topical steroids for cutaneous application and inhaled steroids are permitted.

## 6.2. Permitted concomitant medication and treatment

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

Other treatment that the Investigator considers necessary for a subject's welfare may be administered during the interventional 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 clinical practice guidelines such as the CDC Clinical Practice Guidelines for Vaccination of the Immunocompromised Host.

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

- All prescription and nonprescription medication, vitamins, herbal and nutritional supplements taken by the subject during the 30 days prior to Screening will be recorded.
- All prior anti-cancer treatments, including doses, taken by the subject must be recorded regardless of time.
- All concomitant medications taken while subjects are in the interventional study.

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

### 6.2.1. Contraception

The safety of MAGE-A4$^{c1032}$T during pregnancy and lactation has not been established in humans. The target antigen is known to be expressed on fetal germ line tissues and placenta; therefore, female subjects who are pregnant, intending to become pregnant, or breast feeding are excluded from MAGE-A4$^{c1032}$T studies.

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

- Female subjects of childbearing potential (FCBP) must agree to use an effective method of contraception starting at the first dose of chemotherapy for at least 12 months thereafter and 4 months after the gene modified cells are no longer detected in the blood.
- Male subjects must agree to use an effective method of contraception starting at the first dose of chemotherapy and for 4 months thereafter or longer (if indicated in the country specific monograph/label for cyclophosphamide).

FCBP is defined as premenopausal and not surgically sterilized.

Effective methods of contraception include: intra-uterine device, injectable hormonal contraception, oral 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).

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

# 7. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The Schedule of Procedures is provided in (Section 7.1)for the Interventional Phase of the study and in Table 5 for the LTFU Phase of the study.

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 5)

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

Subjects will be assigned a unique subject number upon signing an informed consent for the Screening Protocol, ADP-0000-001. The number assigned at Screening will serve as the subject ID upon qualification and enrollment into this interventional study.

Study procedures performed as part of standard of care prior to signing informed consent can be used for Screening if they were performed within 7 to 10 days prior to leukapheresis for laboratory tests, and within four weeks prior to Screening for echocardiogram (ECHO)/multiple-gated acquisition scan (MUGA), ECG, pregnancy and infectious disease assays (see Section 7.1 Schedule of Procedures).

## 7.1. Schedule of Procedures

### Table 5: Schedule of Procedures (Interventional Phase)

| | Screening | Leuka-pheresis | Baseline < 7 days prior to chemo | Lymphodepleting Chemotherapy | | | | | T cell infusion | Interventional Phase | | | | | | | | | | | | | | | | End of the Interventional Phase or Withdrawal [1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | Every 3 months[2] | |
| **Day** | | | -14 to -8 | -7 | -6 | -5 | -4 | -3 | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 22 | 29 | 36 | 43 | 57 | 71 | 85 | 127 | 169 | | |
| **Week** | | | | | | | | | | | | | | | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 18 | 24 | | |
| **Visit Window (days)** | | | | | | | | | | | | | +1 | +1 | +3 | | | | | +7 | | | | | ±14 | |
| **Clinical Assessments / Study Procedures[3]** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed Consent[4] | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Baseline Characteristics[5] | | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | | X[6] | |
| Physical Exam | X | | X | | | | | | X | X | X | X | X | X | X | | | | | | | | | | X | |
| Prior/Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[6] | X |
| ECOG Performance Status | X | | X | | | | | | | | | | | X | X | X | X | | X | X | | X | X | X | X | X |
| Vital Signs / Weight | X[7] | | X | | | | | | X[8] | X | X | X | X | X | X | | | | | | | | | | | X |
| Height | | | X | | | | | | | | | | | | | | | | | | | | | | | |

| | Screening | Leuka-pheresis | Baseline < 7 days prior to chemo | Lymphodepleting Chemotherapy | | | | | T cell infusion | Interventional Phase | | | | | | | | | | | | | | | | End of the Interventional Phase or Withdrawal [1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | Every 3 months[2] | |
| **Day** | | | -14 to -8 | -7 | -6 | -5 | -4 | -3 | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 22 | 29 | 36 | 43 | 57 | 71 | 85 | 127 | 169 | | |
| **Week** | | | | | | | | | | | | | | | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 18 | 24 | | |
| **Visit Window (days)** | | | | | | | | | | | | | +1 | +1 | +3 | | | | | | | +7 | | | ±14 | |
| ECG | X[7] | | | | | | | | X | X | | X | | X | X | | | | | | | | | | | |
| Toponin (cTnI or cTnT) | X[7] | | | | | | | | X | X | | X | | X | X | | | | | | | | | | | |
| ECHO/MUGA | X[7] | | | | | | | | | | | | | | | | | | | | | | | | | |
| CT / MRI[9] | X[20] | | X[20] | | | | | | | | | | | | | | | | X | | | X | X | X | X | X |
| CARTOX-10 | | | | | | | | | X[17] | X | X | X | X | X | | | | | | | | | | | | |
| Hematology | X[7] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Lymphocyte subset (CD3, CD4, CD8) | X[21] | | | | | | | | | | | | | | | | | | | | | | | | | |
| Biochemistry | X[7] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | | X | X | X | X | X |
| Coagulation Tests | X[7] | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test | X | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Urinalysis | X[7] | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Infectious Disease[10] | X[7] | | | | | | | | | | | | | | | | | | | | | | | | | |
| Funduscopic Eye Exam | | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Pulse Oximetry | | | X | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

| | Screening | Leuka-pheresis | Baseline < 7 days prior to chemo | Lymphodepleting Chemotherapy | | | | | T cell infusion | Interventional Phase | | | | | | | | | | | | | | | | End of the Interventional Phase or Withdrawal [1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | Every 3 months[2] | |
| **Day** | | | -14 to -8 | -7 | -6 | -5 | -4 | -3 | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 22 | 29 | 36 | 43 | 57 | 71 | 85 | 127 | 169 | | |
| **Week** | | | | | | | | | | | | | | | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 18 | 24 | | |
| **Visit Window (days)** | | | | | | | | | | | | | +1 | +1 | +3 | | | | | +7 | | | | | ±14 | |
| CMV PCR[11] | | | X | | | | | | X | | | | | | X | | X | | X | X | | | | | | |
| Thyroid Function Tests | | | X | | | | | | | | | | | | | | | | | | | | | | | |
| C-reactive protein[12] | | | X | | | | | | X | | | X | | X | X | | X | | | | | | | | | |
| Uric acid | | | X | | | | | | X | | | | | | | | | | | ` | | | | | | |
| GFR/creatinine clearance | X | | X | | | | | | | | | | | X | | | | | | | | | | | | |
| Adverse Events[13] | 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)[14] | | | X | | | | | | | | | | | | | | | | | | | X | | X | X[14] | |
| VSV-G DNA (RCL) for safety[14] | | | X | | | | | | | | | | | | | | | | | | | X | | X | X[14] | |

| | Screening | Leuka-pheresis | Baseline < 7 days prior to chemo | Lymphodepleting Chemotherapy | | | | | T cell infusion | Interventional Phase | | | | | | | | | | | | | | | End of the Interventional Phase or Withdrawal [1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | Every 3 months[2] | |
| **Day** | | | -14 to -8 | -7 | -6 | -5 | -4 | -3 | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 22 | 29 | 36 | 43 | 57 | 71 | 85 | 127 | 169 | | |
| **Week** | | | | | | | | | | | | | | | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 18 | 24 | | |
| **Visit Window (days)** | | | | | | | | | | | | | +1 | +1 | +3 | | | | | +7 | | | | | ±14 | |
| **Leukapheresis, Lymphodepleting Chemotherapy & Investigational Product Administration** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Large Volume Leukapheresis | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Fludarabine | | | | X | X | X | X[23] | | | | | | | | | | | | | | | | | | | |
| Cyclophosphamide | | | | X | X | X | | | | | | | | | | | | | | | | | | | | |
| G-CSF[16] | | | | | | | | X | | | | | | | | | | | | | | | | | | |
| MAGE-A4$^{c1032}$T Infusion | | | | | | | | | X | | | | | | | | | | | | | | | | | |
| Tumor biopsy[18] | | | X | | | | | | | | | | | | | | | | X | | | | | | | X |
| Cell phenotyping and Functional Assays | | | X | | | | | | X[15] | | | X | | X | X | | X | | X | | | X | | X | X | X |
| Cytokine Analyses[12] | | | X | | | | | | X[15,19] | X | X | X | X | X | X | X | X | | X[19] | | | X | | X | X | |
| Collection of ascites or pleural effusion | | | | | | | | | | If fluid develops | | | | | | | | | | | | | | | | |
| Exosome and cf DNA blood collection (liquid biopsy)[22] | | | X | | | | | | | | | | | | | | | X | | | | | | | | X |

| | Screening | Leuka-pheresis | Baseline < 7 days prior to chemo | Lymphodepleting Chemotherapy | | | | | T cell infusion | Interventional Phase | | | | | | | | | | | | | | | | End of the Interventional Phase or Withdrawal [1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | Every 3 months[2] | |
| **Day** | | | -14 to -8 | -7 | -6 | -5 | -4 | -3 | 1 | 2 | 3 | 4 | 5 | 8 | 15 | 22 | 29 | 36 | 43 | 57 | 71 | 85 | 127 | 169 | | |
| **Week** | | | | | | | | | | | | | | | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 18 | 24 | | |
| **Visit Window (days)** | | | | | | | | | | | | | +1 | +1 | +3 | | | | | +7 | | | | | ±14 | |
| Vector Copies (Persistence) for Research | | | | | | | | | | X | | X | | X | X | | X | | X | | | | | | X | X |

1. If a subject withdraws consent or ends the Interventional Phase (i.e. due to progression), all procedures and assessments listed in the completion visit must be performed, unless performed within the previous 30 days. Subjects will continue in the long-term follow-up phase after ending the Interventional Phase. See Section 7.4.9

2. Every 3 months through year 2.

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

4. Written subject informed consent must be obtained prior to performing any of these interventional protocol procedures.

5. Including date of initial diagnosis and primary tumor type, with any relevant histology, stage, or molecular testing results.

6. Only record new medical history and concomitant medications since last visit. Concomitant medications should include mutagenic agents.

7. Study procedures performed as part of standard of care prior to signing informed consent can be used for Screening if they were performed within 7 to 10 days prior to leukapheresis for laboratory tests, and within four weeks prior to Screening for ECHO/MUGA, ECG, pregnancy, and infectious disease assays.

8. 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.

9. CT or MRI scan of the head/neck (if clinically indicated), chest, abdomen and pelvis (if clinically indicated) should be performed (see Section 7.4.7). If a subject is found to have disease progression by imaging, progression should be confirmed by repeat imaging scan performed 4 weeks after the criteria for 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.

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

11. CMV seropositive subjects will continue to be monitored for CMV viremia by CMV DNA PCR until 60 days post infusion (Section 8.2.3).

12. If cytokine release syndrome is suspected, cytokine levels as well C-reactive protein levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

13. If subject has not progressed after one year, only potential gene therapy-related delayed adverse events described in Section 9.4 will be collected from 12 months after infusion.

14. Vector copies for safety samples are collected at Baseline and at Week 12, Week 24, and 1 year post-infusion, then every 6 months post-infusion from year 2-5. RCL samples are collected at Baseline and at Week 12, Week 24, and 1 year post-infusion and then annually.

15. Samples to be collected Day 1 pre-infusion.

16. G-CSF should be given from 24 hours after the last dose of cyclophosphamide in accordance with ASCO guidelines or institutional practice. Long-acting (pegylated) G-CSF may be substituted according to institutional practice as described in Section 8.9.1.

17. CARTOX-10 should be measured on the day of T-cell infusion prior to receiving treatment. Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following T-cell 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.

18. With the exception of subjects for whom there is no safely accessible tumor tissue, core needle biopsies are requested at Baseline (between 2-months and 8 days prior to lymphodepletion), Week 6 (between 3 and 12 weeks), and at progression/withdrawal. Exosome/cfDNA blood sample should be collected in parallel with tumor biopsy collection when possible.

19. Pre-infusion and Week 6 blood collection is for cytokines

20. A CT/MRI scan (or photo for melanoma, if appropriate) must be done within 7 days of lymphodepletion as a Baseline for RECIST 1.1 criteria. For subjects with melanoma cancer and those with known brain metastases, a brain MRI will be performed at Screening for subjects with melanoma cancer and those with known brain metastases and at Baseline or within 1 month prior to lymphodepletion. For all other subjects, brain MRI will be performed at Baseline or within 1 month prior to lymphodepletion. If CNS metastases are detected at Baseline a brain MRI should be performed at all subsequent CT/MRI visits, see Section 7.4.7 Brain Imaging Assessments

21. Lymphocyte subset analysis including CD3, CD4 and CD8 should be performed if locally available. Results are not required prior to leukapheresis.

22. If a tumor biopsy is not performed, liquid biopsy samples are still collected at the indicated visits. To allow for collection in parallel with tumor biopsy, the Baseline liquid biopsy sample may also be taken from two months up to 1 week prior to lymphodepletion. If the post treatment biopsy is collected at or beyond week 6, the liquid biopsy sample will be collected in parallel at that time.

23. Subjects in dose group 3 and expansion group will have another dose of fludarabine on day -4.

## Table 5: 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 (months)** | ± 1 | | | | | | | | | | ± 3 |
| **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 10.2.1. 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 10.2.2.
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.

## 7.2. HLA and Antigen Screening (to be conducted in study ADP-0000-001)

Subjects that are identified by the Investigator as possible candidates for the trial must have completed screening under Screening Protocol ADP-0000-001, to confirm that the subject is HLA-A*02 positive and negative for HLA-A*02:05 in either allele and negative for either HLA-A*02:07 or any A*02 null allele (designated with an "N", e.g., A*02:32N) as the sole HLA-A*02 allele, and have MAGE-A4 positive tumor prior to conducting the remaining study Screening procedures. The Sponsor will review the results of HLA typing for inclusion and exclusion alleles and will adjudicate patient eligibility based on HLA results.

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

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

## 7.3. Screen Failures

A screen failure log documenting the Investigators assessment of each screened subject with regard to the protocols inclusion and exclusion criteria is to be maintained by the Investigator. Subjects may be retested 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) will be recorded at Screening in the subject's medical record and eCRF.

### 7.4.2. Physical Examination and Measurement of Vital Signs

At Baseline, subjects will undergo a physical examination including weight, height and measurement of their vital signs (temperature, pulse, respiratory rate, and blood pressure). The frequency of physical examination, weight and vital signs assessments at subsequent visits is specified in the Schedule of Procedures (Section 7.1)

### 7.4.3. Performance Status

At Baseline, performance status will be measured using the ECOG performance scale (Section 16.2). 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 (Section 7.1)

### 7.4.4. Clinical Safety Assessments

Subjects will be assessed for AEs throughout the study. AEs are to be graded by NCI CTCAE Version 4.0. All AEs must be recorded in the eCRF. Details on assessing and reporting AEs and SAEs are described in Section 9. Safety follow-up procedures for subjects who undergo leukapheresis and do not receive T-cells and for subjects who receive lymphodepleting chemotherapy and do not receive T-cells are provided in Section 4.5.

### 7.4.5. Laboratory Assessments

All laboratory assessments will be performed locally at the site. Laboratory test reference ranges must be provided to Adaptimmune before the study initiates. Refer to Section 16.3 for a listing of laboratory tests.

(FCBP must have a negative pregnancy test at screening and prior to starting lymphodepleting chemotherapy.

Please refer to the Schedule of Procedures (Table 7.1) for additional information regarding the frequency of these assessments.

### 7.4.6. Cardiac Assessments

All cardiac assessments will be performed locally at the site.

The following assessments 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.
- ECG and troponin refer to Section 16.3 for the ECG parameters required. Triplicate ECGs are not required prior to lymphodepletion as long as the subject remains asymptomatic and remains within parameters.

Please refer to Schedule of Procedures (Table ) for information regarding the frequency of these assessments.

### 7.4.7. Brain Imaging Assessments

For subjects with melanoma or known brain metastases, an MRI of the brain with contrast should be obtained at Screening. For all subjects, an MRI of the brain is required at Baseline or within 1 month prior to lymphodepletion to rule out newly diagnosed, untreated brain metastases or to

document stability of previously treated brain metastases. CT with IV contrast may be used only for subjects with contraindications to MRI brain.

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

### 7.4.8. Tumor Response Assessments

Tumor assessments for response and progression will be evaluated at Baseline (within 1 week of chemotherapy), at Weeks 6, 12, 18, and 24, and every 3 months for 2 years and then every 6 months post-infusion or until disease progression and again at completion, according to the RECIST v 1.1 criteria (Section 16.4). The Week 6 scan must be obtained on Day 42±3days. Subsequent scans are to be completed within the visit window permitted in the protocol with the exception or 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 head/neck (if clinically indicated), chest, abdomen and pelvis (if clinically indicated) should be performed at Baseline and all subsequent visits as noted above. Acceptable imaging modalities for this study include:

- Diagnostic-quality CT scan with oral and/or IV iodinated contrast of the chest and abdomen/pelvis, or for subjects with head and neck tumors, head and neck/chest/abdomen (CT is the preferred modality for tumor assessments).
- 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.
- MRI of the brain acquired without and with contrast-enhancement (pre-and post-gadolinium chelate IV), (see below).
- Digital photographs of skin lesions including a ruler for estimating the size of the lesion.

An MRI of the brain with contrast should be obtained at Screening for subjects with melanoma cancer and those with known brain metastases, and at Baseline or within 1 month of lymphodepletion for all subjects. CT with IV contrast may be used only for subjects with contraindications to MRI brain. If CNS metastases are documented at Screening or prior to lymphodepletion, then dedicated CT/MRI scans of CNS metastases should be performed at every on-study tumor assessment, and included as non-target lesions in the tumor worksheet. If CNS metastases are not documented at Screening, then dedicated CNS CT/MRI scans should be performed as clinically indicated. The same imaging modality and image-acquisition protocol (including the use of IV contrast) should be used consistently across all time points for individual subjects to allow uniform comparison of lesions.

Investigators will assess tumor response according to RECIST v1.1 for clinical decision making. Tumor measurements at site should be performed by the same Investigator or radiologist (to the extent that this is feasible). Throughout the study the same imaging technique should be used in order to allow accurate comparisons to be made.

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 will not be assessed before 6 weeks ±3days post infusion (on or after 42 days) of MAGE-A4$^{c1032}$T, unless there is unequivocal clinical evidence of deterioration. Responses or progression should be confirmed by repeat imaging scan performed 4 weeks (on or after 28 days) 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.

### 7.4.9. Long-Term Follow- up

All subjects will be followed for 15 years from time of last T cell infusion for observation of delayed AEs in accordance with FDA and EMA requirements for gene therapy clinical trials [FDA, 2006b; FDA, 2010; EMA, 2009]. These assessments will be collected in the Interventional Phase of this study, and thereafter in the LTFU Phase.

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

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

### 7.4.10. 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, and 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 discontinuing 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 T cell phenotype, function and persistence of the engineered infused cells as well as the evaluation of candidate biomarkers and of immune response, antitumor activity and resistance to therapy. These studies will be performed on blood, tumor biopsies, serum or plasma, fluids and fractionated PBMC collected according to the Schedule of Procedures. All samples will be processed and/or frozen and analyzed either by central laboratory facilities contracted by the Sponsor, or by the Sponsor at the Sponsor's facilities.

Research studies conducted on blood samples may include:

- Flow cytometry to analyze cell subsets and persistence of transduced and non-transduced T cells.
- PCR (polymerase chain reaction) to measure persistence of T cells.
- Genomic sequencing to assess T cell clonality.
- Measurement of serum factors, including, but not limited to cytokines.
- As new technologies and data emerge, other assays relevant to the study objectives may be performed.

Biopsy research studies may include:

- DNA and RNA analysis including PCR and in-situ hybridization to measure infiltration of T cells.
- Genomic sequencing to assess T cell clonality.
- Tissue expression of the target antigen (MAGE-A4).
- Genetic, transcriptomic, and phenotypic analysis of the tumor and tumor microenvironment.
- As new technologies and data emerge, other assays relevant to the study objectives may be performed.

If a subject has an AE, an additional biopsy (e.g., skin, gastrointestinal [GI] tract, bone marrow, tumor) or blood (serum and PBMC) samples may be requested with the objective of gaining an understanding of the underlying etiology of the ongoing AE. The above described research tests may be performed on these samples.

### 7.5.1. Cytokine and Soluble Factors Analysis

Serum is collected at timepoints specified in the Schedule of Procedures (Table ) to allow for measurement of cytokines in the blood. Serum is also collected from subjects with suspected CRS, samples being taken approximately every other day until symptoms are improving or an alternative diagnosis is confirmed. Details regarding serum collection are provided in the Sample Collection Manual.

Serum samples may also be used to detect humoral immune responses to tumor antigens and antibodies to MAGE-A4$^{c1032}$T.

### 7.5.2. Tumor Biopsies

Efficacy of immunotherapy of cancer 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 (e.g. regulatory T cells). 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 6 (between 3 and 12 weeks, at the expected time of an active anti-tumor response by infused T cells) and at disease progression/withdrawal from the study, 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 fresh tissue is provided at Screening through the Screening protocol, and sufficient material is available for research studies, the Baseline biopsy can be omitted. Otherwise Baseline biopsy material should be collected anytime from two months and up to 1 week prior to the start of lymphodepletion, 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. As a guidance and if possible, a responding lesion should be biopsied at the Week 6 time point and a progressing lesion, or a new lesion should be biopsied at the progression time point. The apparent clinical or scan status of the lesion(s) biopsied should be noted at the time (e.g. decreased, stable, increased size).

If feasible, biopsy material should be collected after disease progression on lesions that have progressed.

Additional details regarding the tumor biopsy collection are provided in the Sample Collection Manual.

In subjects who have ascites or pleural effusion, should there be a clinical requirement for removal of the fluid at any time during study, samples are requested to be collected for Adaptimmune for translational research studies.

NOTE: If available, ascites and/or pleural effusion fluid should be collected in addition to, and not instead of, the requested tumor biopsies.

Clinically obtained ascites and/or pleural effusion samples have been shown to be a rich source of tumor cells, tumor infiltrating leukocytes and soluble factors, changes in which have been reported to correlate with disease prognosis and therapy response. Ascites and/or pleural effusion fluid collected in this protocol will be used to interrogate soluble and cellular components of the tumor microenvironment before and after T cell infusion to address mechanisms of sensitivity or resistance to therapy.

### 7.5.3. MAGE-A4$^{c1032}$T 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 long term as a safety measure (Section 10.2.2). Along with the copies of gene-modified DNA per µg DNA, data on the number of transduced cells per µL, or relative to total lymphocyte number will be provided for persistence. [redacted]

- [redacted]

- [redacted]

**7.5.4.** [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

**7.5.5.** [redacted]

[redacted]

- [redacted]
- [redacted]

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

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

# 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. 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 infusion of engineered T cells. The management of these symptoms is suggested but should not necessarily be confined to the below.

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

## 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 carinii Pneumonia

Subjects should receive prophylaxis against Pneumocystis 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 for one year. Other regimens including atovaquone (1500mg daily with food) or aerosolized pentamidine (300 mg every 4 weeks) are also acceptable, e.g. sulfonamide allergy.

### 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

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. If CMV viremia is detected at Baseline, treatment should be initiated prior to lymphodepletion chemotherapy. All CMV seropositive subjects will continue to be monitored for CMV viremia by CMV DNA PCR as shown in Table 7.1 until 60 days post infusion of MAGE-A4$^{c1032}$T. 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 absolute neutrophil count (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 therapy and continued for 6 months. Acceptable regimens include lamivudine (300mg daily), entecavir (0.5mg daily), or tenofovir (300 mg daily).

### 8.2.5. Syphilis

Subjects will be screened for syphilis (Treponema) 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 lymphodepletion 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 x$10^9$/L, hemoglobin >8.0 g/dL (or in accordance with the institutional practice) and as clinically indicated. See AABB Guideline on platelet transfusion [Kaufman, 2015].

### 8.3.1. Irradiated Blood Products

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 lymphodelepting chemotherapy and following lymphodelepting chemotherapy until at least 6 months following IP infusion or until lymphocyte count returns to ≥1.0 x$10^9$/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

Subjects will be screened for CMV seropositivity at study entry. In order to reduce the risk of primary CMV infection all subjects (i.e. both CMV-positive and -negative subjects) should receive leukoreduced blood products where possible (excluding the IP infusion). Where leukoreduced blood is not available, CMV negative subjects must only receive blood products from CMV-seronegative donors from study entry to study completion including during 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 PI should be contacted and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the MAGE-A4$^{c1032}$T cell therapy. If the subject sustains persistent Grade 2, or Grade 3 or 4 autoimmunity, consideration should be given to administration corticosteroid therapy, either topically (e.g. skin, eyes) or systemically, as clinically indicated.

## 8.5. Management of Cytokine Release Syndrome

CRS is a potentially life-threatening toxicity that has been observed following administration of antibodies and ACTs 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. Subjects should be assessed clinically for CRS at all visits according to Section 7.1, Schedule of Procedures. Most cases of CRS present in the two week period following cell infusion. It is important to evaluate the subject for concurrent infections. Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure and disseminated intravascular coagulation. CRS may also be associated with findings of macrophage activation syndrome or occur coincident with tumor lysis syndrome.

CRS 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 6 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical, and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels as described Section 7.5.1 as well C-reactive protein (CRP) levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

**Table 6: 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]<br>• 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<br>• Vigilant supportive care[1].<br>• Assess for infection and treat[2]<br>• Treat hypotension with fluid and pressors<br>• Administer $O_2$ for hypoxia.<br>• Consider administering anti-IL-6 therapy[3] in subjects with extensive co-morbidities or of older age. |
| 3 | Symptoms require and respond to aggressive intervention<br>hypotension requires multiple pressors or high dose pressors<br>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).<br>• Vigilant supportive care[1]<br>• Assess for infection and treat[2]<br>• Treat hypotension with fluid and pressors. Administer $O_2$ for hypoxia.<br>• Administer anti-IL-6 therapy[3] |

| | | |
|---|---|---|
| 4 | Life-threatening symptoms<br>Grade 4 organ toxicity (excluding transaminitis) | • Manage subject in ICU<br>• Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required<br>• 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) and Canadian Product Monograph for tocilizumab recommends a dose of4-8 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 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 refer to the most recent version of the product label for tocilizumab.

## 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 case reports and guidelines for the diagnosis and management of acute GVHD following allogeneic transplant [Dignan, 2012].

### 8.6.1. Diagnosis of GVHD

Subjects should be assessed clinically for GVHD at all visits according to Section 7.1, Schedule of Procedures. The diagnosis of GVHD is predominantly based on clinical findings and is often one of exclusion. 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 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.

| 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, cytokine release syndrome, 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 | 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 |

| | | | |
|---|---|---|---|
| | may result from mucosal ulceration and ileus may ensue. | | |
| Liver | Cholestatic pattern of liver injury including elevated conjugated bilirubin, alkaline phosphatase and GGTP. Subjects may present with jaundice, with pruritus 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. |

Of 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, see 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, GI, and hepatic involvement as described in the table below. Careful measurement of stool volume and assessment of percentage of body area covered by rash are important for proper grading and treatment.

| Stage | Skin | Gut | Liver |
|---|---|---|---|
| 1 | Maculopapular rash <25% of body area | Diarrhea >500 mL/day | Bilirubin 2-3 mg/dL |
| 2 | Maculopapular rash 25% to 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 the table below [Glucksberg, 1974].

| Grade | Skin[a] | Gut[a] | Liver[a] | Functional status[b] |
|---|---|---|---|---|
| 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 |
| [a]Staging is described above<br>[b]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 below, and should be considered in conjunction with input from the consulting physician with bone marrow transplant expertise.

| 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 pruritus. 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*) |
| IV | Methylprednisolone two (2) mg/kg per day* |
| * 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 to 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 GVHD [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 7 days apart.
- 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: absolute neutrophil count <500/μL, absolute reticulocyte count <60,000/μL, and platelet count <20,000/μL, and myelodysplastic syndrome is ruled out. The clinical consequences of aplastic anemia are life-threatening bleeding from thrombocytopenia, and infection as a result of neutropenia. Bacterial and fungal infections are common and a significant cause of morbidity and mortality.

Management of bone marrow suppression and related cytopenias in aplastic anemia is challenging, with no clearly established guidelines regarding immunosuppression. Treatment is largely supportive, including transfusions and treatment of infections. If there is evidence of, or concern for the development of pancytopenia (decreasing hemoglobin, platelets or neutrophils,

or increasing transfusion requirements) following initial bone marrow recovery the following measures should be implemented:

1. Consult a physician with expertise in the management of aplastic anemia
2. Increase the frequency of complete blood counts (CBC) as clinically indicated.
3. Exclude other alternative etiologies such as other drugs, viral causes, etc.
4. An early bone marrow biopsy is recommended for clinical diagnosis, with a sample to be provided to the Sponsor for study. Please refer to Section 7.5 (Correlative Studies and Research Assessments). Details on tissue collections, kit use and shipment information can be found in the Sample Collection Manual.
5. A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the Sponsor.
6. Initiate treatment with G-CSF
7. Consult an Infectious Diseases expert
8. Once alternative etiologies have been excluded, strongly consider immunosuppression (e.g. methylprednisolone 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/infectious diseases consultant(s). If high dose corticosteroids are initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

Please refer to Section 8.6 (Management of Graft-versus-Host Disease) 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, 2018]. CRES typically manifests as a toxic encephalopathy which is generally reversible. Early signs include diminished attention, language disturbance and impaired handwriting. Other signs/symptoms include confusion, disorientation, agitation, aphasia, somnolence, and tremors. In severe cases of CRES (defined as Grade >2), seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral edema may also occur.

CRES occurring within the first 5 days after immunotherapy may be concurrent with high fever and cytokine release syndrome (CRS) symptoms. This form of CRES tends to be of shorter duration, lower grade (Grade 1–2, see Table 9), 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 et al. (2018) have developed a new grading system for ES which incorporates the CARTOX 10‑point neurological assessment (CARTOX‑10) tool, see Table 8. Points are assigned for each of the tasks in Table 8 which are performed correctly. Normal cognitive function is defined by an overall score of 10.

The CARTOX-10 should be used to monitor all subjects for ES.

**Table 8: 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, eg. '*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 7

**Table 9: 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 8 for CARTOX-10.
[2] Papilledema grading is performed according to the modified Frisén scale.
* Based on Neelapu et al. 2018.

### 8.8.2. Monitoring for ES

Brain MRI (or CT scan if MRI not feasible) is recommended at the time of Screening and is required at Baseline for all subjects.

CARTOX-10 should be measured on the day of T-cell 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 T-cell 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 7 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 7: Management of encephalopathy syndrome (ES)**

| Grade | Treatment |
|---|---|
| 1 | For all subjects:<br>• Vigilant supportive care; aspiration precautions; intravenous (IV) hydration<br>• Withhold oral intake of food, medicines, and fluids, and assess swallowing<br>• Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired<br>• Avoid medications that cause central nervous system depression<br>• Evaluate for other contributing causes and treat accordingly<br>Unless symptoms are mild and transient (e.g. 1 point change in CARTOX-10 for less than 12 hours):<br>• 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<br>• Institute levetiracetam therapy and consider EEG if seizure activity is suspected<br>• 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<br>• Anti-IL-6 therapy if associated with concurrent CRS<br>• 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<br>• 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<br>• ICU transfer is recommended<br>• Anti‑IL‑6 therapy if associated with concurrent CRS if not administered previously<br>• 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<br>• 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<br>• 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<br>• Consider neurosurgical consultation for patients with evidence of increased intracranial pressure<br>• ICU monitoring; consider mechanical ventilation for airway protection<br>• Anti‑IL‑6 therapy and repeat neuroimaging as described for Grade 3 ES<br>• 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 fludarabine and cyclophosphamide are included in the product label for the respective drugs. Refer to the most current product labels and Section 6 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 is recommended in all subjects. G-CSF, e.g. filgrastim, should be used for management of neutropenia according to ASCO guidelines [Smith, 2015] G-CSF should be given 24h after the end of lymphodepletion until resolution of neutropenia.

Long-acting (pegylated) G-CSF may be given in preference to short acting daily G-CSF in accordance with institutional standard practice. Pegylated G-CSF will be given as one dose 24h after the end of lymphodepletionon Day 3 post infusion.

# 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 (or designee) is 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 reported to the Sponsor as appropriate. This includes the evaluation of its intensity, the causality between the investigational 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 (Section 7.1 ).

- From date of signing the ICF for this study (interventional protocol) until the day before lymphodepletion chemotherapy starts, only SAEs related to study design/procedures (protocol mandated procedures, invasive tests, or change in existing therapy) *or* AEs leading to withdrawal from the study will be collected.
- All AEs and SAEs will be collected from the start of lymphodepletion chemotherapy until the subject has disease progression following their last cell product infusion.
- Refer to Section 9.4 for details on emerging clinical conditions that must be reported post-infusion. If the subject has not progressed after one year, only those emerging clinical conditions defined in Section 9.4 will be collected from 12 months after T cell infusion. Collection of all AEs/SAEs is no longer required.
- During Long-term Follow-up Phase (15 years post infusion), subjects will only be monitored for those emerging clinical conditions defined in Section 9.4).

## 9.2. Definition of Adverse Event

In accordance with the 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 that 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 of 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 portion of the study, or withdrawal from the study (i.e., both subjects who did and those who did not receive MAGE-A4$^{c1032}$T), serious or severe adverse events will be followed until one of the above criteria is met. Serious adverse events related to investigational product will continue to be recorded and monitored throughout long-term follow-up (see Section 9.4).

### 9.2.1. Assessment of Intensity

Adverse events will be graded according to the NCI CTCAE v 4.0. The Investigator will assess intensity of all AEs using this five point scale (Grade 1 to 5) and record on the eCRF. See Section 8 for guidance on grading of CRS and GVHD.

AEs not specifically listed on the CTCAE should be graded according to Table 8:

**Table 8: 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 investigational product and/or lymphodepleting chemotherapy, 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, 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 that could hypothetically have caused a death had it been more severe).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- 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 that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed 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 include the following:

- Any Grade ≥3 CRS must be reported as an SAE and is subject to expedited reporting.
- Product infusion reactions

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.

**SAEs 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:

- [redacted]
- [redacted]

**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 information as is available. The minimum reporting criteria for an SAE include:

- Identifiable subject (Subject ID)
- SAE
- Toxicity grade
- Suspect investigational product
- Relationship to investigational product
- Identifiable reporting source (PI acknowledgment of the report and signature are required)

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 lymphodepletion chemotherapy.

The SAEW is available in the Study Procedures Manual.

## 9.4. Reporting Criteria during Long Term Follow-Up Phase (Years 1 to 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, 2006b; FDA, 2010; EMA, 2009]. Emergence of any of the following new clinical conditions reported or observed and the action taken will be reported to the Sponsor:

- New malignancies
- New incidence or exacerbation of a pre-existing neurological disorder
  - Excluding all Grade 1 neurologic AEs and Grade 2 AEs assessed as unrelated, unless the Investigator considers clinically significant
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
  - Excluding all Grade 1 autoimmune AEs and Grade 2 AEs assessed as unrelated, unless the Investigator considers clinically significant
  - All rheumatologic disorders will be reported irrespective of grade
- New incidence of 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 or serious infections, Excluding infections secondary to chemotherapy induced cytopenias
- Unanticipated illness and/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 report of the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment.

## 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 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, IRB/ Research Committees (RC) and other study participants. Adaptimmune will comply with country specific regulatory requirements relating to safety reporting to the regulatory authorities, IRBs/RCs 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 an Investigator Safety Letter (ISL).

An Investigator who receives an ISL describing an SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from Adaptimmune will file it with the IB and notify their IRB/RC 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 preclinical or clinical trial data of MAGE-A4$^{c1032}$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 chemotherapy and for at least 12 months after receiving the investigational product, or four months after there is no evidence of persistence/gene modified cells in the Subjects 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 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. A woman who becomes and remains pregnant during the study will be discontinued from the Interventional Phase as exposure to radiation from imaging studies would be contraindicated 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 this protocol should continue to be followed during the long-term follow up.

## 9.8. Preexisting Condition

A preexisting condition is one that is present at the start of the study during Screening. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

## 9.9. Laboratory Test Abnormalities as Adverse Events

Out of range laboratory test results meeting the following criteria, should be reported as adverse events:

- 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 is 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 an SAE.

# 10. SAFETY MONITORING

## 10.1. Safety Review Committee

An Safety Review Committee (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; the Sponsor Pharmacovigilance Physician (this person is not directly involved in the study and will serve as the head of the SRC); the Sponsor Head of Clinical Development, and the Sponsor Head of Statistics. SRC meetings will be conducted approximately monthly provided subjects have been enrolled and data are available to be reviewed. The SRC will review cumulative study safety data and recommend actions regarding cell dose group expansion or dose escalation, study modification for safety reasons, halting and restarting enrollment, study termination, or any other safety related issues deemed important to study conduct, to the Sponsor. An SRC charter, defining roles and accountabilities and the process for safety review, will be available.

## 10.2. Monitoring and Management of Replication-Competent Lentivirus (RCL)

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 animals 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, 2006a; FDA, 2006b; EMA, 2009].

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

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; EMA, 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 the subject must be isolated and no additional subjects treated with MAGE-A4$^{c1032}$T until an action plan is agreed upon as outlined in Section 10.2.

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, National Institute of Health, gene therapy experts, study Investigators, and HIV physician.

### 10.2.1. 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 subject's PBMCs 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 all samples are negative in year one, PBMC samples will be collected and archived annually until 15 years post-infusion. Samples will be archived at Adaptimmune's centralized biorepository.

If a positive VSV-G DNA signal is obtained, the study Investigator will be informed and the subject will be scheduled for a retest as soon as possible and no later than 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 T cells modified with the same vector lot will be postponed. The subject with the confirmed positive VSV-G signal will be scheduled for leukapheresis and a biological RCL test will be performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product [Manilla, 2005].

If the biological RCL test is positive, all infusions using MAGE-A4$^{c1032}$T in the interventional protocol(s) will be halted. An action plan will be discussed with FDA and other regulatory authorities and experts as appropriate. Additional subjects will not be treated with MAGE-A4$^{c1032}$T cells until such time as a plan is completed, reviewed, and agreed upon.

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

### 10.2.2. Testing for Persistence

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidances [FDA, 2006a; FDA, 2006b; EMA, 2009]. Insertional oncogenesis is a theoretical risk in T cells transduced with a lentiviral vector. T cells appear resistant to transformation by integrating viruses [Cattoglio, 2010; Newrzela, 2008]. However, there are cases of oncogenesis with γ-retroviral transduced stem cells. Four of nine subjects with X-linked severe combined immunodeficiency (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; Hacien-Bey-Abina, 2014]. Additionally, two subjects treated for X-linked chronic granulomatous disease (X-CGD) with retroviral transduced stem cells demonstrated insertional activation of the EVI1 transcription factor which resulted in genetic instability, monosomy 7 and clonal progression toward myelodysplasia [Stein, 2010].

#### 10.2.2.1. Testing for Persistence of Gene Marked Cells in Clinical Studies

Peripheral blood mononuclear cells (PBMC) 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 3, 6 and 12 months post-infusion, then every 6 months until 5 years post-infusion and every year from year 6 post infusion in accordance with the FDA and EMA guidances [FDA, 2006a; FDA, 2006b; EMA, 2009]. The samples will be tested using a PCR-based method to detect the presence of the Psi gene, both of which are part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion greater than 1% PBMCs test positive for vector sequences, then the subject's PBMCs will be evaluated for integration site analysis (see Section 10.2.2.2). 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 years 4, 4.5, and 5), no further monitoring of PBMCs is required and collection of samples for persistence may be discontinued. Hematology and chemistry assessments may also be discontinued. NOTE: Samples for RCL must continue to be collected and archived annually until 15 years post-infusion. The 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 is no longer feasible, follow up can be transitioned to a local physician, preferably an oncologist.

#### 10.2.2.2. 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 cell 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, the FDA and other regulators of the findings. If the integration site analysis indicates polyclonality of the genetically modified T cell population, then screening continues as scheduled.

# 11. STATISTICAL AND DATA ANALYSIS

The objectives and endpoints for this study are described in Section 2. This section 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 will be provided in the Statistical Analysis Plan (SAP).

The study will treat subjects using a modified 3 + 3 cell dose escalation design to evaluate DLTs and determine the target cell dose range (see Section 3.2.5 and Section 3.3 for details). Following the dose escalation phase, up to 30 subjects total at the selected dose range (inclusive of subjects accrued during the dose escalation) will be treated across all the eligible tumor types in the dose expansion phase, to characterize and better assess overall safety and anti-tumor activity. Up to an additional 10 subjects will be treated at the selected dose range in the ADP-0044-001R substudy.

Statistical methods for evaluation of ongoing safety using predictive probabilities (described in Section 11.2) are applied to the expansion phase and substudy. The expansion phase and substudy population will be evaluated using the same statistical methods where possible. The dose escalation phase is described in Section 3.2.5 and Section 3.3.2 including the clinical rules for selecting the target dose range and halting the escalation / trial.

Endpoints for safety include DLTs, all AEs, SAEs, clinical and laboratory assessments, prior to ending the Interventional Phase and LTFU AEs.

Subject disposition, RCL and persistence data will also be presented

Endpoints for antitumor activity include ORR (evaluated by RECIST v1.1), BOR, TTR, DoR, DoSD, PFS, and OS.

Summaries of exploratory endpoints, sensitivity analyses, and the handling of missing values including censoring rules along with other details will be described in the SAP.

All summaries will be conducted by cell dose group and across tumor types.

## 11.1. Study Populations

Determination of cell dose group from the dose escalation phase and evaluation of DLT data for both escalation and expansion phase will be based on the dose (group) as received by the subject.

Final study analysis of the data will be assessed according to the following two populations.

**Intent-to-Treat (ITT) Population**: This population comprises all eligible subjects who were enrolled in the trial/substudy. The ITT population is the primary population for safety of the T cell therapy.

**Modified Intent-to-Treat (mITT) Population**: All ITT subjects who received T cell infusion comprise this population. The mITT population is the primary analysis population for safety and antitumor activity endpoints evaluations following MAGE-A4 T cell infusion.

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

## 11.2. Sample Size Calculation

The sample size for both the study and sub-study arebased on clinical judgment; the study is not powered for either primary or secondary endpoints and hence the data will be summarized descriptively. No formal hypothesis testing is planned.

As noted in Section 3.4, up to 30 subjects total at the selected dose group (inclusive of subjects accrued during the dose escalation) will be treated across all the eligible tumor types in the dose expansion phase. Up to 10 additional subjects will be treated in the sub-study. The DLTs in maximum sample size of 30 subjects in the expansion phase plus up to 10 subjects in the sub-study (total maximum number of subjects = 40) will be assessed using Bayesian methods as proposed below.

## 11.3. Assessment of DLTs During Expansion Phase

Bayesian methods, along with frequentist methods, will be employed to assess safety as measured by DLT, to continue treatment of up to 40 subjects in the expansion phase of the study and in the sub-study. The advantage of a Bayesian framework in this small safety oriented study is that, in addition to being able to incorporate prior information, it also allows one to make evaluations without relying on large sample theory.

The DLT rate is defined as the proportion of treated subjects at any time during the study who have at least one DLT. The DLT rate, p, will be evaluated after the expansion phase starts and as subjects accrue in this phase. Subjects on the target dose that were part of the dose escalation will be included in the evaluation during the expansion phase with the maximum sample size set to $N_{max}$=40. DLT rates in excess of 0.33 may be considered as clinically concerning. Bayesian methods are used to evaluate the strength of evidence that the subjects will experience a DLT rate >0.33, if the arm were to proceed to enroll $N_{max}$ subjects.

The number of subjects with at least one DLT, X, in n subjects (in the expansion phase and sub-study) are assumed to follow a binomial distribution, B(n, p). Assuming a fairly non-informative prior distribution, viz., a beta (0.18, 0.82) for the DLT rate, the posterior of the DLT rate follows a beta( 0.18+x, 0.82+n-x) distribution. This then means that the future number of DLTs, Y in m = $N_{max}$ – n, follows a beta-binomial (m, 0.18+x, 0.82+n-x) distribution. Using the methods described in Lee [Lee, 2008] (with θ=0.9), the predictive probability that the DLT rate exceeds 0.33 at $N_{max}$, will be computed as subjects accrue. This probability may be assessed at a threshold of 0.50.

To illustrate this, assume that 6 subjects have been treated in the dose escalation phase at the dose selected for expansion. Bayesian evaluation during the expansion phase begins when the first subject in the expansion phase is treated, thereby n=7. For values of n ≥7 and $N_{max}$ (=40), the predictive probabilities will be computed as X varies to a maximum of n. If the predictive probability meets or exceeds the threshold, (i.e., 0.5), enrollment may be temporarily paused and SRC will conduct a safety review to determine whether enrollment should continue and/or any modifications to the protocol are recommended. Other supportive information, such as the probability that one or more (2 or more etc.) DLTs occur out of the remaining m subjects, the 95% credible interval (based on the posterior distribution) and corresponding 95% (frequentist)

exact confidence interval for the DLT rate may be computed to assist data review by the SRC. Sensitivity to prior distribution will be explored. The information described here along with number and percentage of subjects with DLT will be provided to the SRC.

## 11.4. Statistical Methods

Data from the main study and sub study will be analyzed separately and overall.

### 11.4.1. Safety and Demographic Summaries

Descriptive statistics will be provided for selected demographic and safety assessments by cell dose group 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. In addition the safety and demography data may be presented combining cell dose groups.

The safety profile will be based on AEs reported, vital signs measurements, clinical laboratory measurements, ECG recordings, and physical examination results.

Adverse Events – All AEs will be listed and coded by the Medical Dictionary for Regulatory Activities (MedDRA V21 or above). The number and percentage of subjects reporting any AEs will be tabulated by system organ class and preferred term and categorized by cell dose group. AEs with missing date of onset will also be reported. AEs will be tabulated by severity, relationship to treatment and seriousness. Tables and/or narratives of any on study death, or serious AE, including early withdrawals because of AEs, will be provided should they occur. For subjects with ES, CARTOX-10 will be displayed.

Adverse event data for subjects receiving second infusion will be listed.

Vital Signs – Vital signs will be listed by subject. Summaries of selected vital signs data over time and/or changes from pre-dose values over time may be provided.

Electrocardiogram – ECG data will be listed by subject. Fridericia's or Bazett's correction will be used to compute the corrected QT interval. Summaries of ECG intervals and/or the change from baseline will be provided.

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 version 4. 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.

### 11.4.2. Summary of Antitumor Activity

This section outlines the statistical methods used to summarize the following antitumor activity endpoints across tumors in the final analysis. Where applicable, summaries will be presented by cell dose group. In addition, data may be combined across selected dose groups/sub-study.

Further as lesion data are not captured in the LTFU Phase of the study, all of the following endpoints, except those impacted by death dates, i.e. PFS and OS will be based on Interventional Phase data. However, since subject survival is being collected in the LTFU phase, this information will be used in the analysis of PFS and OS.

Summaries of ORR, BOR, TTR, DoR, DoSD and PFS will use lesion data from first infusion only.

- ORR, defined as the proportion of subjects with a confirmed CR or PR relative to the total number of subjects in the analysis population. The ORR will be based on the assessment of confirmed response per RECIST v1.1.
- BOR, defined as the best response recorded from the date of T cell infusion until disease progression. Response categories from best to worst are: confirmed CR, confirmed PR, SD, and PD and NE (per RECIST v1.1) (see Section 16.4 for details).
- TTR, defined as the duration from T cell infusion to the initial date of the confirmed response.
- DoR, defined as the duration from the initial date of the confirmed response to the date of progressive disease (PD).
- DoSD, defined as the duration from the date of T cell infusion to the date of PD.
- PFS, defined as the interval between the date of first T cell infusion and the earliest date of disease progression or death due to any cause.
  - Since subjects are expected to progress in Interventional Phase (see Section 4.4) before entering LTFU phase, it is expected that most subjects will have a date of disease progression in the Interventional Phase. In the event that the subject did not progress but entered the LTFU phase (for e.g., per Section 4.5.1) death date will be captured from LTFU phase to summarize PFS.
- OS, defined as the time from T cell infusion to death.

Subjects with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the proportion. Two-sided 95% Wilson and exact confidence intervals will be produced to summarize the response data. Response rate may also be summarized within tumor types. In addition, Bayesian 95% credible intervals and posterior mean will be used to describe the response rate in the expansion cell dose group. If p represents the response rate for the TCR, assuming the number of subjects with response = Yes/No, X, in n subjects to follow a binomial distribution, B (n, p), and a non-informative prior distribution, such as a beta (0.1, 0.9) for p, the posterior follows a beta(0.1 + x, 0.9 + n-x) distribution. This posterior will be used to compute the mean and 95% credible interval.

In the expansion cell dose group, time to event endpoints will be summarized and displayed graphically using Kaplan-Meier (K-M) methodology to estimate the median and the 25$^{th}$ and 75$^{th}$ percentiles. OS will be assessed at fixed time points such as 1 year and 2 years using K-M methods.

Censoring Rules:

For DoSD, subjects who do not have a documented disease progression will be censored at the date of the last assessment.

For OS, subjects who are lost to follow-up or still alive will be censored at the date of last contact.

For PFS, subjects who do not have a documented date of disease progression or death will be censored at the date of the last assessment.

The proportion of censored observations will be summarized.

For subjects receiving second infusion:

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

### 11.4.3. Summary of Exploratory Biomarker Endpoints

Biomarker analyses are exploratory and no formal statistical testing will be performed. Descriptive statistics including but not limited to mean, standard deviation and range will be derived where appropriate and graphs may be provided by cell dose group and response. Exploratory biomarker analyses will be described 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.

## 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 and any unused investigational product remaining at the conclusion of the study. Contact the Sponsor or designee 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 that is received at the site from the manufacturer will be stored 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 5.3.2.

## 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 investigational product to ensure:

- Deliveries of 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 sites 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 Electronic Data Capture (EDC) system will be used to collect data pertaining to this trial. Trial data will be captured through an electronic Case Report Form (eCRF). Within the EDC system the eCRF data will be entered by the site staff and all source document verification and data cleaning will be performed by the sponsor or designee (e.g. CRO).

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

The EDC system is a validated software program that has been designed to comply with 21CFR Part 11 requirements. All users will access the system via unique user name and password. A full audit history of all actions performed within the system is maintained. User accounts ensure that each user can only perform the tasks applicable to their role and only have access to the data applicable to their role.

Standard coding dictionaries, WHO Drug and MedDRA will be used to code medications AEs and Medical History.

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

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

## 13.2. Case Report Forms

For each subject enrolled, the completed eCRF must be reviewed and signed by the Principal 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 Source Data

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

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

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

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

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

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

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have direct access to subject source documents to verify the entries on the eCRF. The Investigator (or designee) agrees to cooperate with the monitor (or designee) to ensure 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and any other site level committee deemed appropriate by the institution. Approval from each applicable committee will be received in writing before initiation of the study.

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

## 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 protection to the subject. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) 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. Study Suspension, Study Termination and Study Completion

The Sponsor may suspend or terminate the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that 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 that 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. Clinical Study Report

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

## 15.10. Publication Policy

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

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

# 16. APPENDICES

## 16.1. List of Abbreviations and Definitions of Terms

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

| | |
|---|---|
| ACT | Adaptive T Cell Therapy |
| AE | Adverse event |
| ALK | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| BBB | Bundle branch block |
| BOR | Best overall response |
| BP | Blood pressure |
| CAR | Chimeric Antigen Receptor |
| CBC | Complete blood count |
| CDC | Centers for Disease Control |
| cfDNA | Cell free DNA |
| CFR | Code of Federal Regulations |
| CHF | Congestive heart failure |
| CMV | Cytomegalovirus |
| COPD | Chronic Obstructive Pulmonary Disease |
| CR | Complete response |
| CRP | C-reactive protein |
| CRO | Contract Research Organization |
| CRS | Cytokine release syndrome |
| CSR | Clinical Study Report |
| CT | Computerized tomography |
| CTA | Cancer-testis antigen |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose limiting toxicity |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of response |

| | |
|---|---|
| DoSD | Duration of stable disease |
| EBV | Epstein Barr virus |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| EDC | Electronic Data Capture |
| EDTA | Ethylene-diaminetera acetic acid |
| EGFR | Epidermal growth factor receptor |
| EMA | European Medicines Agency |
| ES | Encephalopathy Syndrome |
| FCM | Flow cytometry |
| FCBP | Female of childbearing potential |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed, paraffin embedded |
| FTIH | First Time In Human |
| 5-FU | 5-Fluorocuracil |
| GCP | Good clinical practice |
| G-CSF | Granulocyte-colony stimulating factor |
| GFR | Glomerular filtration rate |
| GGTP | Gamma-glutamyl transpeptidase |
| GI | Gastrointestinal |
| GLP | Good laboratory practice |
| GMP | Good manufacturing practice |
| GVHD | Graft-Versus-Host Disease |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HLA | Human leukocyte antigen |
| HPV | Human papilloma virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council on Harmonization |
| ICU | Intensive care unit |
| ID | Identifier |

| | |
|---|---|
| IEC | Independent Ethics Committee |
| IFN | Interferon |
| IHC | Immunohistochemistry |
| IL | Interleukin |
| IMRT | Intensity modulated radiation therapy |
| IND | Investigational New Drug application |
| INL | Investigator Notification Letters |
| INR | International normalized ratio |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| mITT | Modified Intent-to-Treat |
| IV | Intravenous |
| K-M | Kaplan-Meier |
| LDH | Lactic acid dehydrogenase |
| LMO2 | LIM domain only 2 |
| LTFU | Long term follow up |
| LTR | Long terminal repeat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHC | Major histocompatibility complex |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MRCLS | Myxoid/Round Cell Liposarcoma |
| MRI | Magnetic resonance imaging |
| MTD | Maximum Tolerated Dose |
| MUGA | Multiple-gated acquisition scan |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| NK | Natural killer cell |
| NS | Normal Saline |
| NSCLC | Non-small cell lung cancer |
| NYHA | New York Heart Association |
| ORR | Overall response rate |
| OS | Overall survival |

| | |
|---|---|
| PBMC | Peripheral blood mononuclear cell |
| PD | Progressive disease |
| PET | Positron emission tomography |
| PFS | Progression free survival |
| PI | Principal Investigator |
| PTT | Partial thromboplastin time |
| PR | Partial response |
| Psi | Packaging signal |
| qPCR | Quantitative polymerase chain reaction |
| RAC | Recombinant DNA Advisory Committee |
| RC | Research Committee |
| RCL | Replication competent lentivirus |
| RCR | Replication competent retrovirus |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic acid |
| RT | Radiation therapy |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SCCHN | Squamous cell carcinoma of the head and neck |
| SCID-X | Severe combined immunodeficiency disease – X linked |
| SD | Stable disease |
| SGPT | Serum glutamate-pyruvate transaminase |
| SIN | Self-inactivating |
| SOP | Standard operating procedure |
| SPEAR | Specific Peptide Enhanced Affinity Receptor |
| SRC | Safety Review Committee |
| SUSAR | Suspected, unexpected serious adverse reactions |
| TCR | T cell receptors |
| TILs | Tumor-infiltrating lymphocytes |
| TKI | Tyrosine kinase inhibitor |
| TTR | Time to response |
| TURBT | Transurethral resection of bladder tumor |
| ULN | Upper limit of normal |

| | |
|---|---|
| USPI | United States package insert |
| VSV-G | Vesicular Stomatitis Virus G glycoprotein |
| WBC | White blood cell |
| WHO | World Health Organization |
| X-CGD | X-linked chronic granulomatous disease |

## 16.2. 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 |

ECOG – Eastern Cooperative Oncology Group

[Oken, 1982]

## 16.3. Laboratory Tests and ECG

| **Hematology, Chemistry and Urinalysis Variables** | |
|---|---|
| **Clinical Chemistry:** | Calcium<br>Phosphorus<br>Magnesium<br>Albumin<br>Bilirubin<br>Alanine aminotransferase<br>Aspartate aminotransferase<br>Alkaline phosphatase<br>Lactate dehydrogenase<br>Sodium<br>Potassium<br>Bicarbonate/$CO_2$<br>Creatinine*Chloride<br>Glucose<br>Urea/BUN<br><br>*24 hour urine test or GFR |
| **Coagulation Screen:** | Prothrombin time *or* International Normalized Ratio<br>Activated partial tissue thromboplastin time |
| **ECG Parameters:** | Heart Rate<br>Heart Rhythm<br>PR Interval<br>RR Interval<br>QRS Interval<br>QTc Interval (Fridericia's or Bazett's correction) |
| **Hematology:** | Red cell count<br>Hemoglobin<br>Hematocrit<br>Mean cell volume<br>Mean corpuscular hemoglobin<br>Mean corpuscular hemoglobin concentration<br>Platelet count<br>White blood cell count & differential count (percent & absolute) |

| | |
|---|---|
| **Lymphocyte subset:** | Absolute cell count and percentage of CD3, CD4, and CD8 (if locally available) |
| **Pregnancy Test:** | Serum beta-HCG or Urine test |
| **Thyroid Function Tests:** | Thyroid Stimulating Hormone |
| **Urinalysis:** | Glucose<br>Ketones<br>Specific gravity<br>Protein<br>Blood<br>Microscopy<br>Bilirubin<br>pH |
| **Infectious Disease:** | HIV 1+2 antibody[#]<br>Hepatitis B surface antigen<br>Hepatitis B core antibody – if positive, test for HBV DNA<br>Hepatitis C antibody – if positive, test for HCV RNA<br>HTLV 1+2 IgG<br>CMV IgG[#]<br>EBV (EBNA)[#]<br>Treponema IgG or RPR [#]<br>**Viral reactivation**<br>CMV DNA PCR – peripheral blood for detection of reactivation. In the event of suspected end organ CMV disease a biopsy may be required<br>[#] Per Institutional Standard Practice is acceptable |
| **Other Tests:** | Uric Acid<br>C-reactive protein<br>Cardiac troponin (cTnI or cTnT – use the same assay consistently for a given subject) |

## 16.4. 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 assessments.

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

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

Cytology and histology can be used in rare cases (e.g., for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease).

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

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

**Measurable lesions**

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

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

**Measurable lesions**

- **Malignant lymph nodes** to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At Baseline and in follow-up, only the short axis will be measured and followed.

- **Lytic bone lesions or mixed lytic-blastic lesions** with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
- **'Cystic lesions'** thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

**Non-measurable lesions**

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites,

pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

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

**Target Lesions**

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

**Non-target Lesions**

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

**Evaluation of Target Lesions**

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

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

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

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

**Special notes on the assessment of target lesions**

- **Lymph nodes** identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if 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'.

**Evaluation of non-target lesions**

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

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

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

**Special notes on assessments for progression of non-target lesions**

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

- **When subject has measurable disease**. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

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

- **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 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:

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** |

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|---|---|---|---|---|
| CR | Non-CR<br>Non-PD | No | PR | ≥4 wks. Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR<br>Non-PD<br>Not evaluated | No | PR | |
| SD | Non-CR<br>Non-PD<br>Not evaluated | No | SD | Documented at least once ≥6 wks. ±3 days from Baseline** |
| Not all Evaluated | Non-PD | No | NE | |
| PD | Any | Yes or No | PD | No prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

*See RECIST 1.1 manuscript 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.

https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf

# 17. LIST OF REFERENCES

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# 18. SUMMARY OF CHANGES – AMENDMENT 07

Amendment 07 Changes

Protocol Amendment 06 dated, 14 March 2019, is replaced by Protocol Amendment 07, dated 04 June 2019. This amendment applies to all participating investigative sites.

**Table 9: Summary of Protocol Changes**

| Section of Protocol | Change/Rationale |
|---|---|
| **Synopsis and Eligibility** | Updated hematologic and renal lab parameters; updated age cap to ≤75 years<br><br>Allow inhaled steroids and remove exclusion for inhaled treatment for respiratory disorders<br><br>Added exclusion language regarding significant history of cardiovascular disorders |
| **1.5.1** | Included justification for reverting to lymphodepletion schedule for Group 3 and Expansion |
| **3.1** | Schematic updated to reflect update in lymphodepletion schedule |
| **3.2.2** | Updated days and doses of lymphodepletion to align with Group 3 regimen. |
| **3.3.1** | Specified that Grade 3 or 4 fever is not a DLT if resolving to grade 2 or below within 72 hours. |
| **5.2** | Table 5, Expansion Dose Group removed. Indicate in Table 4 that Group 3 Lymphodepletion regimen includes Expansion |
| **7.1** | Updated Time and Events Table to reflect updated lymphodepletion regimen |