PROTOCOL NUMBER ADP-0055-002

A PHASE 2 OPEN-LABEL CLINICAL TRIAL OF ADP-A2M4CD8 IN SUBJECTS WITH ADVANCED ESOPHAGEAL OR ESOPHAGOGASTRIC JUNCTION CANCERS

(SURPASS-2 STUDY)

PROTOCOL VERSION: AMENDMENT 2.0

DATE: 17 NOVEMBER 2021

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: A Phase 2 Open-Label Clinical Trial of ADP-A2M4CD8 in Subjects with Advanced Esophageal or Esophagogastric Junction Cancers

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

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: A Phase 2 Open-Label Clinical Trial of ADP-A2M4CD8 in Subjects with Advanced Esophageal or Esophagogastric Junction Cancers

Product Name: ADP-A2M4CD8

Protocol Number: ADP-0055-002

IND Number: 18950

EUDRA Number: 2020-005802-24

DATE OF ORIGINAL PROTOCOL: 13-JANUARY-2021

Amendment Number	Date	Reason for Change
Original	13-Jan-2021	Original version

Amendment Number	Date	Reason for Change
1.0	29-JUN-2021	Addition of futility analysis using Chen 3-stage design Inclusion criterion #5 updated to limit to a maximum of two prior lines of combination or single agent systemic treatment for advanced or metastatic disease before treatment with ADP-A2M4CD8 as the next therapy and to reflect the recent approval of pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy in the first line setting for this patient population. Added secondary endpoint to evaluate efficacy in this population based on investigator radiological assessments. Additional whole blood samples to conduct RNA sequencing to support understanding of the TCR/BCR repertoire at the gene expression level. Correction of errors and omissions from Original Protocol. Updated supportive care guidance, including the treatment of subjects receiving vaccination for or infected with COVID-19. Incorporate protocol administrative letters related to Brain MRI, dated 19Feb2021 and wording of entry criteria, dated 28 Apr2021.

Amendment Number	Date	Reason for Change
2.0	17-NOV-2021	Update to statistical methodology Addition of Pulmonary Function Testing Addition of Inclusion Criteria #14 Update to Exclusion Criteria #8 Addition of Pulse Oximetry for safety assessments Addition of Pulmonary Function Tests to safety assessments Correction to Table 4 lymphodepletion regimen Update to the Management of Cytokine Release Syndrome (CRS)

CONFIDENTIALITY STATEMENT

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

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

DocuSigned by:

[redacted]

17-Nov-2021

Date

Responsible Study Physician/SAE Contact Information

Role	Name	Day Phone and email	After hours phone	Fax Number
Primary Sponsor Study Physician	[redacted]	[redacted]	[redacted]	[redacted]
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Sponsor Details:

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title A Phase 2 Open-Label Clinical Trial of ADP-A2M4CD8 in Subjects with Advanced Esophageal or Esophagogastric Junction Cancers	
Short Title	ADP-A2M4CD8 in HLA-A2^{+} Subjects with MAGE-A4 Positive Esophageal or Esophagogastric Junction Cancers (SURPASS-2)
Protocol Number	ADP-0055-002
Phase	2
Methodology	This is a single treatment cohort study and subjects will be enrolled based upon their tumor type and histology. Subjects with advanced esophageal or esophagogastric junction (EGJ; also called GEJ - gastroesophageal junction) cancers will be enrolled in this study. Based on the tumor histology, this cohort of subjects will have either adenocarcinoma or squamous cell carcinoma type of disease. Subjects with advanced esophageal or GEJ cancers will be pre-screened to determine appropriate HLA and tumor antigen status. Only subjects expressing at least 1 HLA-A*02 inclusion allele and no exclusion allele (Section 4.2.1.1) and whose tumor expresses the melanoma-associated antigen-A (MAGE-A4) antigen by immunohistochemistry (IHC) above a designated cut-off are eligible to undergo further screening for this study. Subjects who sign the Treatment Informed Consent and meet study entry criteria will be enrolled. Enrolled subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the ADP-A2M4CD8 cell Investigational Product (IP). At the discretion of the Investigator and to allow for adequate planning for the subjects to be treated in this protocol, leukapheresis can be performed as soon as possible after the subject is determined to be eligible for study participation. Leukapheresis can be performed prior to initiating second-line treatment regimen or at the end of second-line treatment. Prior to the administration of lymphodepleting chemotherapy, all eligibility criteria will be reconfirmed, baseline tumor assessment will be obtained, and any issues or concerns will be addressed in advance of lymphodepletion, in particular, any factor that might cause or increase the risk of prolonged cytopenia. Where issues are identified, the Investigator is encouraged to adopt mitigation measures such as reduced lymphodepleting regimen or alternative treatment options, if appropriate (Section 6.2). If a subject has progressive disease (PD) and cannot be treatment-free, anti-cancer therapy may be administered between screening and leukapheresis and between leukapheresis and the start of lymphodepletion (bridging therapy), but the required mandatory wash-out periods must be adhered to prior to receiving ADP-A2M4CD8.

	Once the ADP-A2M4CD8 cells are available at the site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 through Day -4) and cyclophosphamide 600 mg/m^2/day for 3 days (Day -7 through Day -5) followed by infusion of ADP-A2M4CD8 cells on Day 1. Subjects will remain hospitalized for observation for at least 24 hours post-T-cell infusion. A longer observation period is allowed as required per the standard of care at the site level or per regional requirements. Subjects will have the following study visits for assessment of eligibility, efficacy, safety, and biomarkers: Pre-screening, Screening, Leukapheresis, Baseline, Lymphodepleting Chemotherapy (Day -7 to Day -4), T-cell infusion (Day 1), immediate post-infusion monitoring (Day 1 through to Day 8), weekly visits until Week 4 post-infusion, then 6, 8, 12, 16, and 24 weeks, then every 2 months until disease progression. An independent external Data Safety Monitoring Board (DSMB) will be responsible for the ongoing monitoring of the safety of subjects during the Interventional phase of the study. The DSMB will review safety data (including adverse events (AEs) and serious adverse events (SAEs), ongoing efficacy data for futility, and overall benefit:risk profile. Subjects will undergo disease monitoring by MRI or CT scan at Screening, Baseline, Week 4, Week 8, Week 12, Week 16, and Week 24, then every 2 months ± 28 days until confirmed disease progression. Once disease progression is established, no further scans will be performed for this study, and subjects will switch to the long-term follow-up (LTFU) schedule of visits at Months 2, 3, and 6 followed by 6 monthly visits through Year 5 and annually thereafter for Years 6 through 15. The time point at which the subject switches to the LTFU assessments/procedures will be driven by the time point at which the subject progresses, for example, if there is disease progression at Week 4, the next visit would be due at Month 2; if there is disease progression at Week 12, the next visit would be due at Month 6. The clinical cut-off for the primary analysis will occur once the last subject dosed has up to 6 months follow-up post-T-cell infusion or has ended the Interventional phase of the study. At this time, all safety and secondary efficacy endpoints will also be summarized to provide supportive evidence to the primary assessment.
Study Duration	Enrollment is expected to be completed in approximately 15 months. The study will be considered complete when all subjects complete 15 years of follow-up, die, or withdraw early from the study.
Study Center(s)	The study will be conducted in approximately 35 sites in North America and Europe. Additional sites may be added at the discretion of the Sponsor.
Number of Subjects	45 subjects

Objectives	Endpoints
Primary: To evaluate the efficacy of autologous genetically modified specific peptide enhanced affinity receptor (SPEAR) T-cells (ADP-A2M4CD8) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced esophageal or GEJ cancers	Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by independent radiological assessment committee
Secondary: To evaluate the safety and tolerability of autologous genetically modified T-cells (ADP-A2M4CD8) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced esophageal or GEJ cancers	• Adverse events (AEs) including serious adverse events (SAEs) • Incidence, severity, and duration of the AEs of special interest • Replication competent lentivirus (RCL) • T-cell clonality and insertional oncogenesis (IO)
To evaluate the efficacy of autologous genetically modified T-cells (ADP-A2M4CD8) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced esophageal or GEJ cancers	• Time to response (TTR) per RECIST v1.1 by independent radiological assessment committee (IRAC), and by investigator radiological assessment • Duration of response (DoR) per RECIST v1.1 by the IRAC, and by investigator radiological assessment • Best overall response (BOR) per RECIST v1.1 by the IRAC, and by investigator radiological assessment • Progression-free survival (PFS) per RECIST v1.1 by the IRAC, and by investigator radiological assessment • Overall survival (OS) • ORR per RECIST v1.1 by investigator radiological assessment.
Development and validation of an *in vitro* diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay
Characterize the surrogates of treatment effect	Peak expansion (i.e., maximum persistence) and time to peak expansion by responder status and overall
Exploratory: [redacted]	• [redacted]
To characterize the tumor and tumor microenvironment pre- and post-T-	• [redacted]

[redacted]	• [redacted] [redacted]
[redacted]	• [redacted] [redacted]

Inclusion Criteria	A Subject must meet the following criteria prior to leukapheresis to be eligible to participate in the study: 1. Subject (or legally authorized representative) has voluntarily agreed to participate by giving written Informed Consent/Assent (as applicable) in accordance with International Council for Harmonization (ICH) GCP guidelines and applicable local regulations. 2. Subject (or legally authorized representative) has agreed to abide by all protocol-required procedures including study-related assessments and management by the treating institution for the duration of the study, including the LTFU. 3. Age ≥ 18 years to < 75 years at the time the Pre-screening Informed Consent is signed. 4. Histological or cytogenetically confirmed diagnosis of advanced (metastatic or inoperable) esophageal or GEJ cancers. 5. Subject has received a maximum of two prior lines of combination or single agent systemic treatment for advanced or metastatic disease before treatment with ADP-A2M4CD8 as the next therapy. a. Esophageal or GEJ cancers Prior therapy requirements in the unresectable locally advanced or metastatic setting: - Subjects should have received a platinum and/or fluoropyrimidine-based regimen (such as FOLFOX). - Subjects may have received anti-PD-1 agent in combination with fluoropyrimidine- and platinum-containing chemotherapy or been offered if available. - Subjects may have been offered taxane-containing regimen, ramucirumab, and/or irinotecan-containing regimen, if available. - Subjects whose tumors are known to be HER2/neu positive should have received or been offered a HER2/neu receptor inhibitor, if available. b. Esophageal squamous cell carcinoma Prior therapy requirements in the unresectable locally advanced or metastatic setting: - Subjects should have received a platinum and/or fluoropyrimidine-based regimen (such as FOLFOX) and may include a taxane-containing regimen, and/or irinotecan-containing regimen. - Subjects whose tumors express PD-L1 or MSI-H/dMMR tumors, should have received or been offered anti-PD-1/anti-PD-L1 therapy if available; unless discussed and agreed upon with the sponsor. 6. Measurable disease according to RECIST v1.1 criteria.

	7. Positive for HLA-A*02:01, HLA-A*02:03, or HLA-A*02:06 allele via Adaptimmune-designated central laboratory testing. HLA-A*02 alleles having the same protein sequence in the peptide binding domains (P group) will also be included. Other HLA-A*02 alleles may be eligible after adjudication with the Sponsor. The Sponsor will review the results of HLA typing for inclusion alleles and will adjudicate subject eligibility based on HLA results. 8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥ 2+ staining in ≥ 30% of the cells by IHC. All samples must have been pathologically reviewed by an Adaptimmune-designated central laboratory confirming expression. 9. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. 10. Left ventricular ejection fraction (LVEF) ≥ 50% or the institutional lower limit of normal range. 11. Fit for leukapheresis and adequate venous access can be established for the cell collection. 12. Female subjects of childbearing potential (FCBP) must have a negative urine or serum pregnancy test AND must agree to use a highly effective method of contraception starting at the first dose of chemotherapy and continuing for at least 12 months or 4 months after the gene modified cells are no longer detected in the blood, whichever is longer. OR Male subjects must be surgically sterile or agree to use a double barrier contraception method or abstain from heterosexual activity with an FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country-specific monograph/label for cyclophosphamide). 13. Must have adequate organ function as indicated by the laboratory values in the table below:

	System / **Laboratory Value**
	Hematology
	ANC: ≥ 1.5 x10^9/L (without granulocyte-colony stimulating factor [G-CSF] support)
	Platelets: ≥ 100 x10^9/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
	Hemoglobin: ≥ 90 g/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
	Coagulation
	Prothrombin Time or International Normalized Ratio: ≤ 1.5 x upper limit of normal (ULN) unless receiving therapeutic anticoagulation
	Partial Thromboplastin Time (PTT): ≤ 1.5 x ULN unless receiving therapeutic anticoagulation
	Renal
	Glomerular Filtration Rate or Creatinine Clearance (CrCl) (Estimated or Calculated)[1]: ≥ 50 mL/min
	Hepatic
	Serum Total Bilirubin: ≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin < 35% of total bilirubin) Exception: Subjects with liver metastasis ≤ 2.5 x ULN
	ALT/AST: ≤ 2.5 x ULN Exception: Subjects with liver metastasis ≤ 5.0 x ULN
	[1] Renal function (GFR) will be estimated or measured according to standard practice at the treating institution. Renal function will be reassessed at Baseline using the same methodology.
	14. Subjects must have ≥ 90% room air oxygen saturation test at rest at Screening (within 7 days of leukapheresis) and at Baseline.
Exclusion Criteria	A subject meeting any of the following criteria is not eligible for participation in the study:

1. Positive for HLA-A*02:05 in either allele via Adaptimmune-designated central laboratory testing. HLA-A*02 alleles having the same protein sequence as HLA-A*02:05 in the peptide binding domains (P groups) will also be excluded. Other alleles may be exclusionary after adjudication with the Sponsor.
2. Received or plans to receive the following 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
Tyrosine kinase inhibitor (e.g., dabrafenib, trametinib, and vemurafanib)	1 week	1 week
Immune therapy (including monoclonal antibody therapy and checkpoint inhibitors)	2 weeks	4 weeks
Anti-cancer vaccine	8 weeks in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months.	8 weeks in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months.
Gene therapy using an integrating vector	Use of previous gene therapy using a Lentiviral vector is permitted only if transduced T-cells represent less than 1% of peripheral blood mononuclear cell (PBMC) (< 1500 copies of vectors per microgram of PBMC DNA) at the time of screening. Eligibility testing must be done by Adaptimmune's designated Contract	Not permitted after leukapheresis and prior to lymphodepletion

		Research Organization (CRO).	
	Corticosteroids or any other immunosuppressive therapy. Note: Use of topical steroids is not an exclusion. See Section 6.5 for exceptions.	2 weeks	2 weeks
	Anti-MAGE-A4 therapy Note: Fresh screening biopsy post anti-MAGE-A4 therapy must be obtained to confirm MAGE-A4 positivity.	2 weeks	2 weeks
	Investigational treatment or interventional clinical trial	4 weeks	4 weeks
	Allogeneic hematopoietic stem cell transplant	Not permitted within any amount of time	Not permitted within any amount of time
	Radiotherapy to the target lesions	N/A	3 months. A lesion with unequivocal progression may be considered a target lesion regardless of time from last radiotherapy dose. (Note: There is no wash-out period for palliative radiation to non-target organs).
	Major surgery	N/A	4 weeks. Subjects must have recovered from any surgically related toxicities.
	Note: Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician.		

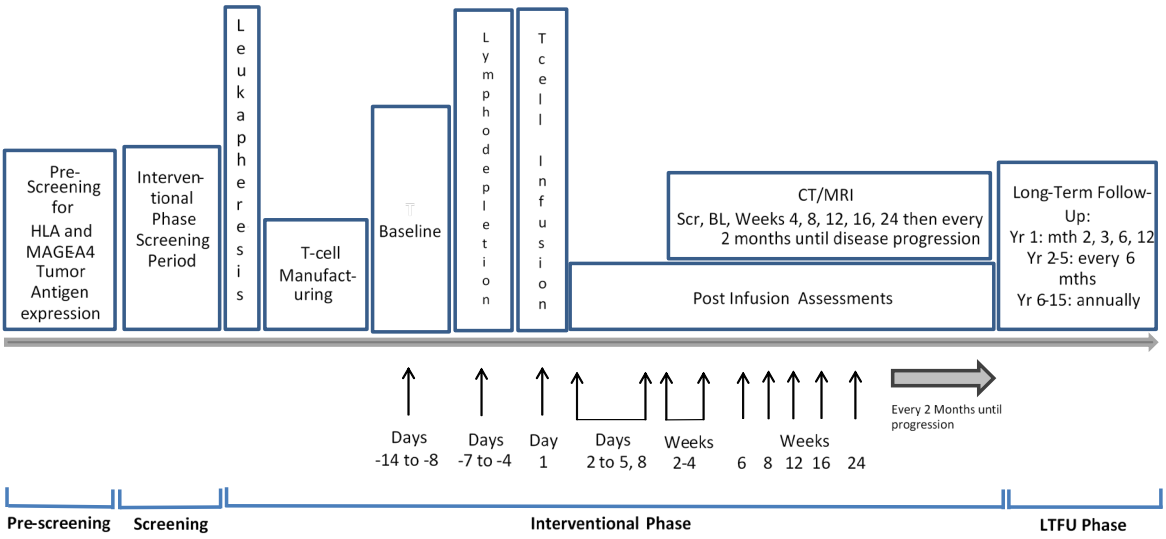
	3. Toxicity from previous anti-cancer therapy must have recovered to ≤ Grade 1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia and vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g., peripheral neuropathy) can be enrolled. 4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide, or other agents used in the study. 5. History of autoimmune or immune-mediated disease. Subjects with hypothyroidism, diabetes, adrenal insufficiency, or pituitary insufficiency that are stable on replacement therapy are eligible. Subjects with disorders such as asthma, psoriasis, or atopic dermatitis that are well controlled without requiring systemic immunosuppression are also eligible. 6. Leptomeningeal disease, carcinomatous meningitis, or symptomatic central nervous system (CNS) metastases. Subjects with a prior history of symptomatic CNS metastases must have received treatment (i.e., stereotactic radiosurgery and whole brain radiation or surgery) and be neurologically stable for at least 1 month, not requiring anti-seizure medications and off of steroids for at least 14 days prior to leukapheresis and lymphodepletion. Anti-seizure prophylaxis is permitted. Subjects who have asymptomatic CNS metastases without associated edema, shift, requirement for steroids, or anti-seizure medications for the treatment of seizures are eligible. REGIONAL REQUIREMENT IN UK: Leptomeningeal disease, carcinomatous meningitis, or symptomatic CNS metastases. 7. Any other prior malignancy that is not in complete remission. Resectable squamous or basal cell carcinoma of the skin is acceptable. Prior malignancies that have been surgically resected and show no evidence of disease are acceptable. 8. Uncontrolled intercurrent illness including, but not limited to: • Ongoing or active infection • COVID-19 infection or a positive COVID-19 Real-Time Polymerase Chain Reaction (RT-PCR) test within 28 days of leukapheresis or lymphodepleting chemotherapy. If subject has had a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart • Clinically significant pulmonary disease with any one pulmonary function parameter < 60% predicted (FEV1 or TLC

	or DLCO) assessed prior to leukapheresis and within 2 months of the start of lymphodepleting chemotherapy • Requirement for oxygen support (for cardiac or pulmonary disease) • Clinically significant cardiac disease defined by congestive heart failure New York Heart Association Class 3 or Class 4 • Uncontrolled clinically significant arrhythmia • Acute Coronary Syndrome (angina or myocardial infarction) in last 6 months • Congenital or family history of long QT syndrome or a history of torsade de pointes • Current uncontrolled hypertension despite optimal medical therapy • History of stroke or CNS bleeding; transient ischemic attack or reversible ischemic neurologic deficit in the last 6 months 9. Active infection with HIV, HBV, HCV, or HTLV as defined below: • Positive serology for HIV. • Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months. • Active hepatitis C infection as demonstrated by hepatitis C RNA test. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT-PCR or branched DNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value. • Positive serology for HTLV 1 or 2. • Re-screening for infectious disease markers is not required at Baseline (prior to lymphodepletion) unless > 6 months has elapsed. 10. Pregnant or breastfeeding. 11. In the opinion of the Investigator, the subject is unlikely to fully comply with protocol requirements.

Investigational Product, Dose, Route, and Regimen	ADP-A2M4CD8 is the SPEAR TCR product administered at a dose of 1.0 x 10^9 to 10 x 10^9 transduced cells by a single intravenous infusion on Day 1.
Comparator Therapy	None
Statistical Methodology	The main analysis for the primary efficacy endpoint ORR will be based on Chen's three stage design [Chen, 1997], extending the methods outlined in [Jung, 2004] and [Koyama, 2008] to a three-stage design. The primary endpoint for efficacy is ORR defined as the proportion of subjects with a confirmed complete response (CR) or confirmed partial response (PR) per RECIST v1.1 via IRAC review, relative to the total number of subjects in the analysis population. The primary analysis population for safety and efficacy will be the modified intent-to-treat (mITT) population defined as all subjects who received T-cell infusion. Null Hypothesis (H_0): $p \leq p_0$ vs. Alternate Hypothesis (H_1): $p > p_0$, where p_0 (historical ORR) = 0.14. Statistical assumptions include: • The assessment for efficacy will be based on the mITT population using confirmed ORR via RECIST v1.1 per the IRAC. • The type I error (α) will be no more than 0.049. • The type II error (β) will not exceed 0.1. • Exact binomial methods will be used to test the hypothesis. Based on the statistical design assumptions above, approximately 45 subjects will be enrolled according to a Chen's three-stage design. • First Stage: 15 evaluable subjects will be enrolled in stage 1. The predefined ORR is met if there are 2 or more confirmed complete response (CR) or confirmed partial response (PR) out of the first 15 evaluable subjects based on investigator radiological assessment. Subject enrollment will continue to the next stage if there is a demonstrable clinical benefit from treatment with cell therapy and there are no major safety concerns. Otherwise, subject enrollment will be stopped. The independent DSMB will make this recommendation. The DSMB will review safety data (including AEs and SAEs), ongoing efficacy data for futility, and overall benefit:risk profile, and make a recommendation to Adaptimmune. The process for the review will be defined in the DSMB charter • Second Stage: An additional 13 evaluable subjects will be enrolled in stage 2, if the predefined ORR is met (i.e., 7 or more responses, confirmed CR or confirmed PR, out of the first 28 (15 + 13) evaluable subjects based on investigator radiological assessment), then the study will continue to the third and final stage.

	Subject enrollment will continue to the next stage if there is a demonstrable benefit from treatment with cell therapy and there are no major safety concerns. Otherwise, subject enrollment will be stopped. The independent DSMB will make this recommendation. • Third Stage: An additional 17 evaluable subjects will be enrolled for a total of 45 (15 + 13 +17) evaluable subjects. A DSMB charter, defining roles and accountabilities and the process for review, will be available prior to the start of the study. The primary endpoint, ORR by RECIST v1.1 by an independent radiological assessment committee, will be evaluated using Clopper-Pearson (exact Binomial) 2-sided 95% confidence intervals (CIs). The key secondary efficacy endpoints TTR, DoR, BOR, PFS, and OS will be summarized. No hypothesis testing is planned for these secondary endpoints. 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. 2-sided Ninety five (95)% confidence intervals will be produced. Overall Survival may be assessed at fixed time points such as 1 year and 2 years using K-M methods. Descriptive statistics will be provided for demography, safety, surrogates of treatment effect, health outcomes using the EQ-5D-3L, and laboratory assessments. 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. Other subgroups may be explored, and these will be described in the Statistical Analysis Plan.

1.2. Schema


Pre-Screening for HLA and MAGEA4 Tumor Antigen expression
Interven-tional Phase Screening Period
Leukapheresis
T-cell Manufact-uring
Baseline
Lymphodepletion
T cell Infusion
CT/MRI
Scr, BL, Weeks 4, 8, 12, 16, 24 then every 2 months until disease progression
Post Infusion Assessments
Long-Term Follow-Up:
Yr 1: mth 2, 3, 6, 12
Yr 2-5: every 6 mths
Yr 6-15: annually
Days -14 to -8
Days -7 to -4
Day 1
Days 2 to 5, 8
Weeks 2-4
6
8
12
16
Weeks
24
Every 2 Months until progression
Pre-screening
Screening
Interventional Phase
LTFU Phase

1.3. Time and Events Table

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

Written Informed Consent must be obtained prior to performing any protocol procedures. A Pre-screening Informed Consent form (ICF) will be signed prior to obtaining a blood sample for HLA testing and tumor tissue for antigen testing. The Treatment ICF will be signed prior to all other study procedures (Section 8).

Table 1: Main T&E Table

			Interventional Phase																							
	Pre-screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**End of Interventional Phase or Study Withdrawal**	**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**			
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**± 1 day**					**± 3 days**				**± 7 days**				**± 1 mo**	**n/a**	
Day				**-14 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**29**									
Week															**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**			
Informed Consent	X	X																							Section 10.1.4
Demographics	X	X																							Section 8.1.1
Inclusion/Exclusion	X	X		X																					Section 5.2 and Section 5.3
Disease history/Tumor type	X	X																							Section 8.1.2
Document tumor-specific mutations	X	X																							Section 8.1.2
HLA[16]	X																								Section 8.2.1
MAGE-A4 Antigen	X																								Section 8.2.2

			Interventional Phase																							
	Pre-screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**End of Interventional Phase or Study Withdrawal**	**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**			
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**± 1 day**					**± 3 days**				**± 7 days**				**± 1 mo**	**n/a**	
Day				**-14 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**29**									
Week															**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**			
Safety and Efficacy Assessments																										
Medical history		X																								Section 8.4.1
Physical examination		X		X					X					X	X											Section 8.4.2
Prior anti-cancer therapies		X	X	X																						Section 8.4.3
Prior and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.4
ECOG		X		X										X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.5
Height				X																						Section 8.4.7
Weight		X		X													X		X	X	X	X		X		Section 8.4.7
Vital signs		X		X					X[2]	X	X	X	X	X	X								X	X		Section 8.4.6
Pulse Oximetry		X[18]		X																						Section 8.4.8
ECG		X		X					X	X			X													Section 8.4.9.1
ECHO/MUGA		X																								Section 8.4.9.2
CT/MRI		X		X													X[3]		X[3a]	X[3a]	X[3a]	X	X[3]	X		Section 8.3.1
Brain MRI		X[4]		X[4a]																						Section 8.4.10
Hematology		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.12
Renal function (GFR estimated or measured)		X		X																						Section 8.4.11

			Interventional Phase																							
	Pre-screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**End of Interventional Phase or Study Withdrawal**	**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**			
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**± 1 day**					**± 3 days**				**± 7 days**				**± 1 mo**	**n/a**	
Day				**-14 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**29**									
Week															**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**			
Clinical chemistry		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.13
Coagulation		X		X																					Section 8.4.14
Pregnancy test		X		X																					Section 8.4.17
Infectious disease screening		X															X[5]		X[5]		X[5]				Section 8.4.18
Pulmonary function tests		X		X[17]																					Section 8.4.9.4
CMV PCR				X[6]					X[6]						X[6]		X[6]	X[6]	X[6]						Section 8.4.19
Thyroid function tests				X																					Section 8.4.15
C-reactive protein[7]				X					X			X		X	X		X								Section 8.4.21
Ferritin[7]				X					X			X		X	X		X								Section 8.4.22
ICE Assessment									X	X	X	X	X	X											Section 8.4.20
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.5
Leukapheresis, Lymphodepleting Chemotherapy, and Investigational Product Administration																									
Leukapheresis			X																						Section 6.1
Fludarabine[15]					X	X	X	X[9]																	Section 6.2
Cyclophosphamide					X	X	X																		Section 6.2
ADP-A2M4CD8 infusion									X																Section 6.3.2

			Interventional Phase																							
	Pre-screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**End of Interventional Phase or Study Withdrawal**	**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**			
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**± 1 day**					**± 3 days**				**± 7 days**				**± 1 mo**	**n/a**	
Day				**-14 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**29**									
Week															**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**			
Biomarker Assessments																									
Tumor biopsy[10]				X													X[10a]					X[10b]		X	Section 8.6.1
Cytokine and soluble protein analyses				X					X[11]	X		X		X	X	X	X		X	X		X	X		Section 8.6.2
Liquid biopsy (blood plasma)				X					X[12]								X[10]			X		X[10]		X	Section 8.6.3
Gene expression analysis (whole blood)				X					X								X[14]			X[14]				X[14]	Section 8.6.4
Fluids (ascites/pleural)				X (if fluid develops)																					Section 8.6.1
Cell phenotyping and functional assays				X					X[12]					X	X		X		X	X		X	X	X	Section 8.6.5
Persistence (vector copies)		X[8]		X						X		X		X	X		X		X	X		X	X		Section 8.4.23
RCL (VSV-G DNA)				X																X		X	LTFU		Section 8.4.24
Subject Reported Outcomes																									
EQ-5D-3L				X															X		X	X	See footnote[13]		Section 8.7

[1] Screening Visit assessments should be completed within 28 days of leukapheresis; CT/MRI scans and ECHO/MUGA scans performed as standard of care within 4 weeks prior to Screening Visit (prior to study consent) are acceptable.

[2] Vital signs are measured pre-infusion, at 5, 15, and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.

[3] The Week 4 scan may occur within +3 days but not before Week 4 (Day 29). [3a] On study scans from Week 4 through Week 16 should be at least 28 days apart to ensure compliance with RECIST v1.1 requirement for confirmatory scans in the event that an objective response is noted by the independent radiological assessment committee (IRAC). For scans every 2 months, these can be ± 28 days.

[4] Regional requirement in UK - A Screening Brain MRI is required in regions where subjects with leptomeningeal disease, carcinomatous meningitis or central nervous system (CNS) metastases are excluded.

[4a]This is required at Baseline and must be within 1 month prior to lymphodepletion.

[5] Subjects who are HBV core antibody positive at Screening will have HBV DNA assessments at Week 4, 8, and 16.

[6] If subjects are CMV seropositive at Screening, CMV PCR is done at Baseline. All CMV seropositive subjects will continue to be monitored by CMV PCR at Day 1 and Weeks 2, 4, 6, and 8.

[7] If CRS is suspected, CRP, ferritin, and cytokine levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

[8] This is only for a subject who has previously received a gene therapy using a Lentiviral vector. Subjects must have results below the lower limit of quantification for at least 2 samples taken at least 1 month apart. At least one of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.

[9] Begin G-CSF 24 hours after the last dose of lymphodepleting chemotherapy and continue as per Section 6.2.3.

[10]Tumor biopsy and liquid biopsy should be collected at the same visit within 24 hours of each other. 10[a] can be taken anytime between Week 3 and Week 8; 10[b] can be taken at Week 24 ± 4 weeks.

[11]Day 1 cytokine samples are to be collected pre-infusion and 2 to 4 hours post-infusion.

[12] This is collected pre-infusion.

[13]EQ-5D-3L will also be done at Month 12 if the subject remains in the Interventional phase of the study.

[14] Whole blood collection to be performed on the same day as the tumor biopsy procedure.

[15] Fludarabine dose must be adjusted for renal impairment in accordance with parameters in Section 6.2.1.

[16] Subjects that provide a buccal swab sample may also need to provide a confirmatory blood sample for HLA testing.

[17] Only required if the PFT is not within 2 months of the start of lymphodepleting chemotherapy.

[18] Screening oxygen saturation must be done within 7 days of leukapheresis.

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

Table 2: T&E for Long-Term Follow-Up

Time Post-infusion	**Year 1**				**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Years 6–15**	**Comments**
Months	**2**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**Annually**	
Visit Window			**± 1 month**										**± 3 months**	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.2
Anti-cancer therapies, including mutagenic agents and other investigational agents	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.4
LTFU adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.5.8
Adverse events	X													Section 8.5
Hematology	X	X	X	X		X		X		X		X	X	Section 8.4.12
Clinical chemistry	X	X	X	X		X		X		X		X	X	Section 8.4.13
Vector copies (persistence)	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.23
VSV-G DNA (RCL)		X	X	X		X		X		X		X	X	Section 8.4.24

2. INTRODUCTION

2.1. Study Rationale

2.1.1. Rationale for Using ADP-A2M4CD8 in Esophageal or Esophagogastric Cancers

Adoptive T-cell therapy 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 adoptive T-cell therapy [Kalos, 2013; Klebanoff, 2016; Maus, 2014; Morgan, 2010; Rosenberg, 2008].

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, melanoma-associated antigen-A (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 messenger RNA (mRNA) expression in the range of 30% to 50%. CTAs often have coordinated expression, with several expressed in a single tumor [Gure, 2005]. In addition to RNA, immunohistochemistry (IHC) is often used to determine the expression levels of CTAs. While it is generally seen that mRNA expression of these antigens correlates well with protein expression, it should be noted that there is frequent heterogeneous expression of protein across the tumor, with strong expression in a small subset of tumor cells. Epigenetic and post-transcriptional modifications determine protein expression levels under certain conditions.

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

ADP-A2M4 specific peptide enhanced affinity receptor (SPEAR) T-cells are genetically engineered to target the subject's MAGE-A4 positive tumor in the context of the appropriate HLA expression. ADP-A2M4CD8 are autologous cluster of differentiation (CD) 4- or CD8-positive T-cells that have been transduced with a self-inactivating (SIN) Lentiviral vector expressing a high affinity MAGE-A4 specific TCR and a CD8α. MAGE-A4 is a CTA that has restricted expression in normal tissue and is expressed across a range of solid tumors at varying frequencies.

ADP-A2M4CD8 recognizes the MAGE-A4$_{230-239}$; GVYDGREHTV peptide derived from the MAGE-A4 family of CTAs. Thus, ADP-A2M4 incorporates an affinity-enhanced TCR capable of recognizing the HLA-A*02-GVYDGREHTV antigen complex.

The safety and efficacy of the next-generation ADP-A2M4CD8 have been shown in subjects with several different tumor types in an ongoing phase 1 study ADP-0055-001 (NCT04044859). As of 01 October 2020, 6 subjects (1 with Myxoid/Round Cell Liposarcoma [MRCLS], 2 with gastroesophageal junction (GEJ) cancers, 1 with ovarian cancer, 1 with head and neck squamous cell carcinoma, and 1 with esophageal cancer) have been treated with ADP-A2M4CD8 (range ~1 to 5.7 billion transduced cells). To date, 1 subject with GEJ cancer had a partial response (PR per Response Evaluation Criteria in Solid Tumor [RECIST]) and has had progression-free survival (PFS) > 6 months. One subject with head and neck cancer also had a PR. All other subjects have had BOR of stable disease (SD). No dose limiting toxicities (DLTs), or serious adverse events (SAEs) have been reported. ADP-A2M4CD8 SPEAR T-cells have shown an acceptable safety profile, and subjects with GEJ cancer and head and neck cancer have demonstrated evidence of anti-tumor activity. Translational data and early clinical results indicate that co-expression of the CD8α co-receptor on CD4+ SPEAR T-cells may increase the potency of the product by conferring additional killing activity to the helper T-cell subset. Further information is detailed in the ADP-A2M4CD8 Investigator's Brochure.

2.2. Background

2.2.1. ADP-A2M4CD8 SPEAR T-cell Background

The 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%. CTAs often have coordinated expression, with several expressed in a single tumor [Gure, 2005].

Table 3: MAGE-A4 Expression in Various Cancer Types

MAGE-A4 Screening by IHC (Data From 05 June 2017 Through 24 May 2020)[1]		
Tumor Types	**# Evaluable Subjects Tested**	**No ≥ 30% at ≥ 2 + IHC (%)**
Esophageal Carcinoma	55	10 (18%)
• Adenocarcinoma	48	7 (15%)
• Squamous cell carcinoma	6	2 (33%)
• Adenosquamous carcinoma	1	1 (100%)
GEJ Adenocarcinoma	48	11 (23%)

[1] Data obtained from the ADP-0000-001 Screening protocol in support of ADP-0055-001, ADP-0044-001, and ADP-0044-001R and from ADP-0044-002

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 T-cells from apoptosis and contribute to the development of tumors by promoting survival [Yang, 2007].

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

ADP-A2M4CD8 are autologous CD4- or CD8-positive T-cells that have been transduced with a self-inactivating Lentiviral vector expressing a high affinity MAGE-A4 specific TCR and an additional wild-type CD8α co-receptor. The CD8α co-receptor, which differentiates ADP-A2M4CD8 from ADP-A2M4, is designed to provide additional functionality to CD4 T-cells.

[redacted]

2.2.2. Discovery of ADP-A2M4CD8

Several peptides derived from MAGE proteins have been identified by mass spectroscopy from tumor cell lines, including the HLA HLA-A*02-restricted peptide MAGE-A4$_{230-239}$

(GVYDGREHTV). HLA Class I molecules are involved in the presentation of antigenic peptides on tumors to T lymphocytes. The prevalence of HLA subtypes varies from population to population, with 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 [Allele Frequency Net Database, 2020]. 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. A full description of the clinical program and studies conducted can be found in the ADP-A2M4CD8 Investigator's Brochure.

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

The addition of a CD8α co-receptor directly impacts TCR binding to the HLA-peptide complex in CD4+ T-cells, thereby enhancing CD4+ T-cell effector function. ADP-A2M4CD8 cells do not display any new cross-reactivity, and transduced T-cells do not display additional alloreactivity *in vitro*. As expected, alloreactivity from both ADP-A2M4 and ADP-A2M4CD8 was only seen towards 2 HLA-A*02:05 positive cell lines. Therefore, subjects who are HLA-A*02:05 positive will be excluded from the study. Subjects with either HLA-A*02:07 or any A*02 null allele as the sole HLA-A*02 allele will be also excluded due to decreased activity with these alleles. No additional alloreactivity was noted, and importantly, no targets induced an enhanced alloreactive response from ADP-A2M4CD8 cells. Together, these data demonstrate that addition of the CD8α co-receptor does not alter the specificity of the ADP-A2M4 TCR. Details regarding design and preclinical testing of ADP-A2M4CD8 are provided in the ADP-A2M4CD8 Investigator's Brochure.

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

2.2.3. Current Therapies for Esophageal or Esophagogastric Junction Cancers Emerging Data from ADP-A2M4CD8 and Other TCRs

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

In Western countries, the incidence of adenocarcinoma of the esophagus and GEJ is rising rapidly, while the incidence of squamous cell carcinoma of the esophagus is declining owing to a decrease in tobacco use. The estimated combined incidence and mortality of esophageal and gastric cancers in 2018 in the United States (US) are 43,710 and 26,650 cases, respectively [Cancer Facts and Figures, 2016]. Many subjects present with advanced disease, which is a stage associated with 5-year survival of only 5% to 15% and median survival of 8 to 10 months. The 2019 NCCN guidelines outline the principles of systemic therapy regimens recommended for advanced esophageal or GEJ adenocarcinoma, which may be used interchangeably (with some exceptions) [NCCN, 2019]. The mainstay of treatment for advanced disease is fluoropyrimidine (combined with oxaliplatin or cisplatin) and/or platinum-based combination chemotherapy. Low response rates and high levels of toxicity are observed with second-line chemotherapy.

The selection of regimens for second-line or subsequent therapy is dependent on prior therapy and performance status. Based on the available data and FDA approvals, the guidelines have included the targeted therapy of ramucirumab (category 1 for GEJ adenocarcinoma and category 2A for esophageal adenocarcinoma) as a single agent or in combination with paclitaxel (preferred) as treatment options for second-line or subsequent therapy [Fuchs, 2014; Wilke, 2014].

Second-line or subsequent therapy depends on prior therapies and Performance Status (PS). Nivolumab was recently approved for the treatment of subjects with advanced esophageal squamous cell carcinoma as combination therapy with fluoropyrimidine and platinum therapy in the first line setting. Trastuzumab prolongs survival in subjects with HER2/neu overexpressing gastric cancer (10% to 30% of gastric cancer) in first-line chemotherapy, and addition of the anti-VEGFR-2 antibody ramucirumab in second line improves overall survival (OS) and PFS when compared to chemotherapy alone [Orditura, 2014]. There is some evidence that esophagogastric cancer can respond to immunotherapy [Kim, 2005; Popiela, 2004; Ralph, 2010], but no other treatments beyond palliative chemotherapy are available for subjects with advanced disease. Pembrolizumab was recently approved as part of combination therapy in the first line setting for subjects with recurrent locally advanced or metastatic, gastric, or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test. A recently published phase 3 trial (TAGS) has shown activity for the combined regimen of trifluridine and tipiracil in metastatic gastric and GEJ adenocarcinoma in the third-line setting [Shitara, 2018]. It is noted that this treatment should be considered for a very select population of subjects with low-volume GEJ adenocarcinoma who have minimal or no symptoms and the ability to swallow pills. Other recommended regimens for third-line or subsequent therapy for esophageal and GEJ cancers include regimens recommended for second-line therapy that were not previously used and pembrolizumab for adenocarcinomas with PD-L1 expression levels by CPS of ≥ 1.

In the pivotal study, KEYNOTE-059, the efficacy of pembrolizumab was studied in subjects with gastric or gastroesophageal junction adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Among 143 subjects that expressed PD-L1 with a CPS ≥ 1, the overall response rate (ORR) for pembrolizumab was 13.3% (95% confidence interval [CI]: 8.2, 20.0) [Keytruda package, June 2020].

The efficacy of pembrolizumab in subjects with locally advanced or metastatic esophageal squamous carcinoma who progressed on or after at least 2 prior systemic treatments was investigated in KEYNOTE-180. For 63 subjects, the observed ORR was 14.3% (95% CI: 6.7%, 25.4%) (PMID: 30570649). Additional clinical evidence suggests that the historical ORR for therapies administered to subjects who progressed on or after at least 2 prior systemic therapies for esophageal and GEJ cancers is 14%.

Emerging evidence of third-line systemic treatment in advanced/metastatic gastric cancer supports the efficacy of systemic treatment in refractory gastric cancer beyond second-line treatment. Established third-line therapies include chemotherapies (irinotecan, taxane, and TAS-102), tyrosine kinase inhibitors (apatinib and regorafenib), and immune-checkpoint inhibitors (nivolumab and pembrolizumab). Given the expanding options for third-line therapies, there is an unmet need for clinicians to individualize treatment [Chan, 2019]. Tumor -specific biomarker stratification is likely to be relevant to targeted and immunotherapy approaches. However, it is not yet used for subject stratification or selection. Future studies are warranted to focus more on gene signaling to guide subject selection.

ADP-A2M4CD8 SPEAR T-cells have shown an acceptable safety profile, and subjects with GEJ cancer and head and neck cancer have demonstrated evidence of anti-tumor activity. Translational data and early clinical results indicate that co-expression of the CD8α co-receptor on CD4+ SPEAR T-cells may increase the potency of the product by conferring additional killing activity to the helper T-cell subset. This dose escalation trial is ongoing and updated clinical and translational data will be presented [Hong, 2020].

2.3. Benefit/Risk Assessment

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

2.3.1. Benefit

The estimated combined incidence and mortality of esophageal and gastric cancers in 2018 in the US are 43,710 and 26,650 cases, respectively [Cancer Facts and Figures, 2016]. Many subjects present with advanced disease, which is a stage associated with 5-year survival of only 5% to 15% and median survival of 8 to 10 months. Given the very low survival rates in esophageal and gastric cancer, there is a high degree of unmet need across the board.

Clinical evidence suggests that the historical ORR for therapies administered to subjects who progressed on or after at least 2 prior systemic therapies for esophageal and GEJ cancers is 14%. This historical ORR will be used to evaluate the efficacy of ADP-A2M4CD8. Preliminary evidence from the ADP-0055-001 study suggests that ADP-A2M4CD8 treatment in this subject population may result in an ORR of 35% (Section 9).

Furthermore, preliminary safety data from the phase 1 Protocol ADP-0055-001 suggests that the ADP-A2M4CD8 SPEAR T-cells have an acceptable safety profile, and subjects with gastroesophageal cancers and head and neck cancer have demonstrated clinical responses. Five of 6 subjects demonstrated initial tumor shrinkage. This trial is ongoing in an expansion cohort of subjects [Hong, 2020].

The benefit of ADP-A2M4CD8 is not known at present, however, the MAGE-A4 antigen is highly expressed in the proposed tumor types. An objective response has been observed in protocol ADP-0055-001 following treatment with ADP-A2M4CD8; therefore, the potential therapeutic benefit of ADP-A2M4CD8 is being investigated in this phase 2 trial.

Several clinical trials investigating the efficacy and safety of adoptive T-cell therapy with Adaptimmune's TCRs are ongoing. Efficacy has been demonstrated with other adoptive T-cell therapies, including NY-ESO-1^{c259}T and ADP-A2M4 [Rapoport, 2015; Merchant, 2015; Araujo, 2019; D'Angelo, 2018a; Mackall, 2017].

MAGE-A4 positivity (≥ 30% at ≥ 2 + IHC) is expressed in esophageal squamous cell carcinoma (33%), esophageal adenocarcinoma (15%), GEJ adenocarcinoma (23%), and esophageal adenosquamous carcinoma (100%) (Table 3).

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

2.3.2. Risk

The safety and tolerability of ADP-A2M4CD8 is being assessed in the phase 1 study ADP-0055-001 (NCT04044859) across multiple tumor types including esophageal and GEJ cancers as described in Section 2.1. Toxicities observed with ADP-A2M4CD8 are common to other TCR or chimeric antigen receptor (CAR)-T therapies, checkpoint inhibitors, or standard of care chemotherapies.

Toxicities such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and prolonged or recurrent pancytopenia are specific to TCR and CAR-T therapies; therefore, guidelines for management of these events are included in this protocol (Section 10.4). TCR therapy is generally administered once; most toxicities resolve within 4 to 6 weeks after T-cell infusion.

Alloreactivity, whereby TCRs reactive towards a given peptide-major histocompatibility complex display cross-reactivity towards different HLA allelic variants, is a theoretical risk. Preclinical data indicate strong anti-HLA-A*02:05 alloreactivity, making A*02:05 an exclusion allele. Data also indicate decreased potency against MAGE-A4$_{230-239}$ peptide when presented by HLA-A*02:07; therefore, subjects with A*02:07P alleles are ineligible unless they also express an inclusion allele. Preclinical studies support the specificity, safety, and anti-tumor activity of ADP-A2M4CD8; therefore, an unacceptable risk of off-target reactivity is not expected. No evidence of alloreactivity has been detected in the ongoing phase 1 study to date.

The study incorporates several measures to address the risks including the following:

1. Extensive preclinical evaluation of the ADP-A2M4CD8, which has incorporated learnings from other adoptive T-cell therapy programs ADP-A2M4CD8 Investigator's Brochure.]

2. Based on the preclinical alloreactivity data, exclusion of subjects with HLA-A*02:05 in either allele or with HLA-A*02 alleles having the same protein sequence as HLA-A*02:05 in the antigen binding domains (P groups)
3. Use of a validated clinical trial assay for the selection of subjects with MAGE-A4 expression in their tumors
4. Treatment in specialized academic centers experienced with the management of toxicities associated with autologous T-cell therapies
5. Protocol guidelines for management of toxicities including CRS, ICANS, and pancytopenia/aplastic anemia as well as preventive measures for infectious complications
6. A Data Safety Monitoring Board (DSMB) to evaluate safety during the study

2.3.3. Overall Benefit: Risk Conclusion

Subjects with advanced esophageal or GEJ cancers who have received 2 prior lines of therapy constitute a population with a high unmet medical need given the aggressive nature and poor survival rates. In the clinical setting, the response rates generally decrease with increasing lines of therapy. Responses are rare in the third-line setting. Given the lack of standard of care in the third line, there is not a single benchmark in this setting. The limited effective third-line treatment options create the opportunity for innovative new therapies for expedited approvals.

The potential risks identified in association with ADP-A2M4CD8 are justified by the anticipated benefits that may be afforded to subjects; therefore, the benefit/risk for ADP-A2M4CD8 supports initial testing in the clinic in the defined study population. A phase 1 clinical study with ADP-A2M4CD8 and preclinical studies support the specificity, safety, and anti-tumor activity of ADP-A2M4CD8 T-cells. Measures to ensure safe administration of ADP-A2M4CD8 have been included in this study protocol, with close monitoring for toxicities and guidelines for their management by an external, independent DSMB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
To evaluate the efficacy of autologous genetically modified SPEAR T-cells (ADP-A2M4CD8) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced esophageal or GEJ cancers	ORR per RECIST v1.1 by independent radiological assessment committee
Secondary:	
To evaluate the safety and tolerability of autologous genetically modified T-cells (ADP-A2M4CD8) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced esophageal or GEJ cancers	• Adverse events (AEs) including serious adverse events (SAEs) • Incidence, severity, and duration of the AEs of special interest • Replication competent lentivirus (RCL) • T-cell clonality and insertional oncogenesis (IO)
To evaluate the efficacy of autologous genetically modified T-cells (ADP-A2M4CD8) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced esophageal or GEJ cancers	• Time to response (TTR) per RECIST v1.1 by independent radiological assessment committee (IRAC), and by investigator radiological assessment • Duration of response (DoR) per RECIST v1.1 by the IRAC, and by investigator radiological assessment • Best overall response (BOR) per RECIST v1.1 by the IRAC , and by investigator radiological assessment • PFS per RECIST v1.1 by the IRAC, and by investigator radiological assessment • OS • ORR per RECIST v1.1 by investigator radiological assessment
Development and validation of an *in vitro* diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay

Objectives	Endpoints
Characterize the surrogates of treatment effect	Peak expansion (i.e., maximum persistence) and time to peak expansion by responder status and overall
Exploratory	
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a phase 2, open-label study of genetically engineered ADP-A2M4C8 in HLA-A*02 subjects with MAGE-A4 expressing metastatic or inoperable (advanced) esophageal or GEJ cancer.

All subjects will be enrolled into one treatment cohort based upon their tumor type and histology. Subjects with advanced esophageal or GEJ cancers will be enrolled in this study. Based on the tumor histology, this cohort of subjects will have either adenocarcinoma or squamous cell carcinoma type of disease. [Redacted] [Chen, 1997].

[Redacted]

4.1.1. Pre-screening

Subjects must be aged ≥ 18 years and ≤ 75 years and must have a diagnosis of advanced (metastatic or inoperable) esophageal or GEJ cancers to be eligible for Pre-screening.

Subjects will sign a pre-screening ICF and undergo initial screening for the relevant HLA-A alleles and MAGE-A4 tumor antigen as part of this study.

At sites that employ remote consent at pre-screening, it is the responsibility of the Investigator to obtain written or remote consent in accordance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved processes and any local requirements in advance of providing subjects with an HLA buccal/cheek swab test and/or sending tissue for MAGE-A4 test. This allows subjects to be pre-screened for HLA and MAGE-A4 antigen without requiring travel to a clinical study site. The HLA buccal swab kit contains a self-administered buccal/cheek swab, and relevant instructions would be sent to subjects who have provided written or remote consent in accordance with IRB/IEC-approved processes and any local requirements. Any subject determined to be eligible based on results from the buccal swab would still undergo confirmatory HLA genotyping on a blood sample during pre-screening.

4.1.2. Screening

Subjects who have been identified as positive for the relevant HLA alleles and MAGE-A4 tumor antigen will be asked to sign the treatment ICF and enter Screening to determine full eligibility for this study. Screening assessments should be completed within 28 days of leukapheresis; CT/MRI scans and echocardiogram (ECHO)/multiple-gated acquisition (MUGA) scans, performed as standard of care within 4 weeks prior to Screening Visit 2 (i.e., prior to treatment consent), are acceptable.

4.1.3. Enrollment

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

Enrolled subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the ADP-A2M4CD8 cell IP. At the discretion of the Investigator and to allow for adequate planning for the subjects to be treated in this protocol, leukapheresis can be performed as soon as possible after the subject is determined to be eligible for study participation. Leukapheresis can be performed prior to initiating second-line treatment regimen or at the end of second-line treatment. Anti-cancer therapy may be administered to subjects between Screening and leukapheresis and between leukapheresis and the start of lymphodepletion. However, following the manufacture of a subject's cells, a subject must receive IP as the next therapy. In the event an exception has been granted for early leukapheresis, a subject must receive the IP as the third line of therapy; otherwise, subject may receive IP as second line of therapy after discussion with the sponsor. If, in the opinion of the Investigator, the subject requires immediate therapy after leukapheresis, the subject may receive bridging therapy for the period during which the subject is awaiting the manufacture of IP. Following this bridging therapy, the subject must adhere to the mandatory wash-out periods (Section 5.3) prior to receiving ADP-A2M4CD8. In addition, subjects must continue to have measurable disease following the bridging therapy in order to receive ADP-A2M4CD8.

Prior to the administration of lymphodepleting chemotherapy, all eligibility criteria will be reconfirmed, baseline tumor assessment will be obtained, and any issues or concerns are addressed in advance of lymphodepletion, in particular, any factor that might cause or increase the risk of prolonged cytopenia. Where issues are identified, the Investigator is encouraged to adopt mitigation measures such as reduced lymphodepleting regimen or alternative treatment options, if appropriate. Once the ADP-A2M4CD8 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 through Day -4) and cyclophosphamide 600 mg/m^2/day for 3 days (Day -7 through Day -5) (Section 6.2), followed by infusion of ADP-A2M4CD8 cells on Day 1 (Section 6.2.3). The lymphodepleting chemotherapy may be given as an outpatient treatment, or subjects may be hospitalized at the discretion of the Investigator. Guidelines for this decision are provided in Section 6.2.

The T-cell infusion will be given as an inpatient procedure. Subjects will remain hospitalized for observation for at least 24 hours post-T-cell infusion. A longer observation period is allowed as required per the standard of care at the site level. Discharge following T-cell infusion will be at the discretion of the Investigator. All subjects must be reviewed by the Investigator (or a designated Study Physician) prior to discharge.

REGIONAL REQUIREMENTS (UK and France): Subjects will remain hospitalized for observation for at least 10 days post-T-cell infusion, based on regional requirements.

Efficacy, safety, health-related outcome, and biomarker assessments to be conducted at each visit are outlined in the Time and Events (T&E) tables (Table 1 and Table 2). Efficacy will be assessed by both Investigators and independent physicians using RECIST v1.1. To allow time for the immune response to become apparent and for potential transient inflammatory reaction of

the disease to the treatment ("tumor flare"), response will not be assessed before 1 month post-infusion of ADP-A2M4CD8. Therefore, imaging scans should not be performed earlier than 4 weeks post-infusion unless there is unequivocal clinical evidence of deterioration.

Subjects will continue to have scans for efficacy during the Interventional phase of the study until disease progression is established. Once progression is established, no further scans will be performed for this study, however, subjects will continue to be followed for observation of delayed AEs (Table 2) in accordance to FDA and EMA requirements for gene therapy clinical trials [FDA, 2020a; FDA, 2010; EMA, 2009].

Subjects will be seen in the clinic for evaluation according to the Main T&E table (Table 1) until disease progression, death, or withdrawal.

Subjects who end the Interventional phase of the study will undergo assessments/procedures according to the long-term follow-up (LTFU) T&E Table (Table 2). The time point at which the subject switches to the LTFU assessments/procedures will be driven by the time point at which the subject progresses, for example, if there is disease progression at Week 4, the next visit would be due at Month 2; if there is disease progression at Week 12, the next visit would be due at Week 24 (Month 6).

A subject will be considered to have ended the study when he/she has been followed for 15 years of follow-up, died, or withdraw early from the study.

4.2. Scientific Rationale for Study Design

This is a phase 2, open-label clinical trial with ADP-A2M4CD8 SPEAR T-cells in subjects with advanced esophageal or GEJ cancers who are HLA-A*02 positive and tumors that express MAGE-A4.

The ongoing ADP-A2M4CD8 phase 1 study, ADP-0055-001 SURPASS, revealed an encouraging safety profile and treatment response in different cancer types. As of 01 October 2020, 6 subjects (1 with MRCLS, 2 with GEJ cancers, 1 with ovarian cancer, 1 with head and neck squamous cell carcinoma, and 1 with esophageal cancer) have been treated with ADP-A2M4CD8 (range ~1 to 5.7 billion transduced cells). To date, 1 subject with GEJ cancer had a PR per RECIST and has had PFS > 6 months. One subject with head and neck cancer also had a PR. All other subjects have had BOR of SD. No DLTs were noted. Two subjects reported SAEs and were deemed related to the IP. ADP-A2M4CD8 SPEAR T-cells have shown an acceptable safety profile, and subjects with GEJ cancer and head and neck cancer have demonstrated evidence of anti-tumor activity. Translational data and early clinical results indicate that co-expression of the CD8α co-receptor on CD4+ SPEAR T-cells may increase the potency of the product by conferring additional killing activity to the helper T-cell subset.

This phase 2 study, ADP-0055-002, is to further evaluate the efficacy, safety, and tolerability of autologous genetically modified SPEAR T-cells (ADP-A2M4CD8) specifically in subjects with advanced esophageal or GEJ cancers.

This study will be a non-comparative study with a primary efficacy endpoint of ORR per RECIST v1.1 by the IRAC. ORR will be based on confirmed (tumor) responses per RECIST v1.1 by the IRAC.

Clinical evidence suggests that the historical ORR for therapies administered to subjects who progressed on or after at least 2 prior systemic therapies for esophageal and GEJ cancers is 14%. This historical ORR will be used to evaluate the efficacy of ADP-A2M4CD8 by hypothesis testing. Preliminary evidence from the ADP-0055-001 study suggests that ADP-A2M4CD8 treatment in this subject population may result in an ORR of 35% (Section 9).

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

4.2.1.1. HLA

Subjects must express at least 1 inclusion HLA-A allele (such as A*02:01P, A*02:03P, or 02:06P), which is defined as having proven capacity to bind the target peptide and ability to activate the ADP-A2M4 T-cells specifically in the presence of that peptide (i.e., absence of alloreactivity). There may be other HLA-A*02 alleles that may be eligible for inclusion after adjudication with the Sponsor. The adjudication process will be documented.

HLA-A*02:07 has been shown to have a reduced affinity for the target peptide but has not shown any alloreactivity. Therefore, subjects positive for HLA-A*02:07P (as well as subjects positive for any null A*02 allele, designated with an "N" suffix (e.g., A*02:32N), are ineligible unless they also express one of the inclusion alleles (e.g., a subject expressing both A*02:01 and A*02:07 is eligible).

Due to the risk of alloreactivity, subjects positive for HLA-A*02:05P in either allele are ineligible. Other alleles may be exclusionary after consultation with the Sponsor.

To ensure that the subject possesses the appropriate HLA-A*02 alleles, HLA testing of a blood sample is required. HLA genotyping will be performed at a central reference laboratory using an FDA approved sequence-based typing (SBT) HLA genotyping assay.

Despite HLA-A*02 being the most common HLA allele group in the western world, its expression varies greatly among populations of different races and ethnicities. With a significant proportion of subjects expected to be excluded based on HLA status, an optional buccal swab kit may be offered to subjects prior to the Pre-screening Visit at participating sites. This allows subjects to be screened for HLA without requiring travel to a clinical study site. The kit, containing a self-administered buccal/cheek swab and relevant instructions, would be sent to possible subjects who have provided written or remote consent in accordance with IRB/IEC -approved processes and any local requirements. Any subject determined to be eligible based on results from the buccal swab would still undergo confirmatory HLA genotyping on a blood sample during pre-screening.

4.2.1.2. MAGE-A4 Expression in Tumor

MAGE-A4 positivity (≥ 30% at ≥ 2 + IHC) is expressed in esophageal squamous cell carcinoma (33%), esophageal adenocarcinoma (15%), GEJ adenocarcinoma (23%), and esophageal adenosquamous carcinoma (100%). High expression of MAGE-A4 has been reported across several cancer indications, including lung, esophageal, head and neck, bladder, ovarian, breast, and colorectal cancers [Tajima, 2003; Forghanifard, 2011; Errington, 2012; Barrow, 2006; Alves, 2007; Cuffel, 2011; Kocher, 2002; Daudi, 2014; Otte, 2001; Cabezón, 2013].

MAGE-A4^{c1032} T-cells have been shown to produce strong IFNγ responses against tumor cell lines expressing high MAGE-A4 mRNA levels (> 10,000 MAGE-A4 transcripts). Since no adequate models to define the threshold of MAGE-A4^{c1032} T-cell activation are currently available, this protocol will select for subjects with high MAGE-A4 expression. As such, Adaptimmune will be using a conservative cut-off (≥ 2+ in ≥ 30% of tumor cells) to ensure sufficient expression of the antigen.

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

Optional remote consent to ADP-A2M4CD8 testing is permitted for any clinical site that has the necessary written or verbal consent processes in place and has obtained the relevant IRB/IEC and local approvals. This allows subjects with archival specimens available to consent for ADP-A2M4CD8 testing without requiring travel to a clinical study site.

4.2.2. T-cell Manufacturing

ADP-A2M4CD8 is autologous CD4 and CD8 T-cells engineered with an affinity-enhanced TCR to target the tumor antigen MAGE-A4. Autologous T-cells are obtained from eligible subjects who have antigen-positive tumors and who have appropriate HLA-A genotype. The CD4 and CD8 T-cells are transduced with an SIN Lentivirus vector expressing the CD8α MAGE-A4 (affinity-enhanced clone 1032) under Good Manufacturing Practice conditions. The product of this transduction is polyclonal T-cells that are designed to target MAGE-A4 in tissue. The transfer SIN Lentiviral vector has been meticulously designed to contain only the minimal genetic elements required for function and no vector proteins for maximum biosafety [Dull, 1998]. Many reports provide evidence supporting the relative biosafety of SIN Lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the Lentivirus long terminal repeat in comparison to the γ-retroviral vectors [Montini, 2006; Maruggi, 2009; Modlich, 2009; Montini, 2009].

Cell product is typically ready to be returned to the site within 1 month after the start of manufacturing. Receipt of T-cell product at the clinical site is required before the start of lymphodepleting chemotherapy.

4.2.3. Lymphodepletion

Prior to the administration of lymphodepleting chemotherapy, all eligibility criteria will be reconfirmed, baseline tumor assessment will be obtained, and any issues or concerns are addressed in advance of lymphodepletion, in particular, any factor that might cause or increase the risk of prolonged cytopenia. Where issues are identified, the Investigator is encouraged to adopt mitigation measures such as reduced lymphodepleting regimen or alternative treatment options, if appropriate (Section 6.2).

Lymphodepletion, typically achieved by the administration of cytotoxic chemotherapy consisting of fludarabine in combination with cyclophosphamide, prior to autologous cell transfer may enhance immune reconstitution by the transferred cells and increase tumor-specific responses. Immune reconstitution is enhanced through homeostatic mechanisms that facilitate expansion of T lymphocytes [Baccala, 2005] and facilitate trafficking of the engineered T-cells

[Pinthus, 2004]. Lymphodepletion also enhances the activity of the adoptively transferred cells via the removal of inhibitory factors such as regulatory T-cells [Wolf, 2003] and can activate antigen presenting cells through the induction of inflammatory cytokines and induction of tumor apoptosis with resulting cross presentation of tumor antigens to T-cells.

Evidence suggests that preparation for successful engraftment and expansion of gene-modified adoptive cellular therapy depends on the specific action of some cytotoxic drugs. In this regard, fludarabine is specifically T-cell depleting and has shown in multiple CAR-T hematological cancer studies to improve T-cell expansion, persistence, and disease-free survival when compared to cyclophosphamide [Turtle, 2015]. Cyclophosphamide was administered at 30 to 60 mg/kg x 1 day and fludarabine at 25 mg/m^2/day x 3 to 5 days. Effective lymphodepletion has also been demonstrated in other CAR-T-cell studies using reduced cyclophosphamide dosing together with fludarabine [Batlevi, 2016].

Based on Adaptimmune's experience using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy in the ADP-0044-001 MAGE-A4 study (NCT01343043) and the ADP-0055-001 (SURPASS) study's (NCT04044859) increasing evidence that fludarabine is a key component of the adoptive T-cell therapy, the lymphodepleting regimen in this study consists of intravenous (IV) fludarabine 30 mg/m^2/day for 4 days (Day -7 through Day -4) and cyclophosphamide 600 mg/m^2/day for 3 days (Day -7 to Day -5). This lymphodepleting regimen has previously demonstrated acceptable safety and efficacy in a study of ADP-0044-001 MAGE-A4 in subjects with multiple tumor types.

4.2.4. Long-Term Follow-Up

Subjects exposed to gene therapies may be at risk for delayed AEs when there is persistent biological activity. Contributing factors for delayed adverse events include persistence of viral vector, integration of genetic material into host genome, prolonged expression of transgene, and alterations in the expression of host genes. The LTFU evaluation in the study is designed to adhere to the FDA and EMA guidance for LTFU of subjects in gene therapy clinical trials [FDA, 2020a; FDA, 2020b; FDA, 2010; EMA, 2009], and it involves monitoring of subjects who have been exposed to Lentivirus -mediated gene transfer in this clinical study for 15 years. Further information on the safety monitoring for the theoretical risks associated with the use of Lentiviral vectors and potential for IO as well as safety monitoring are available in Section 8.4 and Section 10.7.

4.3. Justification for Dose

The cell dose of ADP-A2M4CD8 is within the range of 1 x 10^9 to 10 x 10^9 transduced cells, administered by a single intravenous infusion. If the transduced cell dose is less than the minimum dose, manufacturing of additional transduced T-cells from excess banked leukapheresis product is undertaken to achieve a total dose in the target range. Doses below the minimum transduced cell dose of 1 x 10^9 will not be administered.

The safety and tolerability of ADP-A2M4CD8 are being assessed in the ongoing phase 1 trial of multiple tumor types including esophageal or GEJ cancers. Subjects were treated with ADP-A2M4CD8 (dose range of ~1 to 10 billion transduced cells). ADP-A2M4CD8 SPEAR T-cells

have shown an acceptable safety profile, and subjects with GEJ cancer and head and neck cancer have demonstrated evidence of anti-tumor activity.

Across the development program, doses of up to 10 x 10^9 have been administered and well tolerated. Most of the adverse events noted were consistent with those typically experienced by cancer subjects undergoing cytotoxic chemotherapy or cancer immunotherapy.

4.4. End of Study Definition

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

5. STUDY POPULATION

Subjects will be assessed for and must meet eligibility for study participation prior to leukapheresis (i.e., at Screening [Visit 2]), prior to manufacturing where leukapheresis has been stored AND prior to lymphodepleting chemotherapy (i.e., at Baseline).

5.1. HLA and Antigen Pre-screening

To be eligible for pre-screening, subjects must be aged ≥ 18 years to ≤ 75 years with a diagnosis of advanced (metastatic or inoperable) esophageal or esophagogastric cancer confirmed by either histology or cytogenetics.

Subjects identified by the Investigator as possible candidates for the study must complete preliminary screening to determine HLA and tumor antigen status. Only subjects with an appropriate HLA-A genotype and whose tumor expresses the MAGE-A4 antigen above the cut-off according to the applied IHC are eligible to undergo Screening (Visit 2) for this study.

5.2. Inclusion Criteria

A subject must meet the following criteria prior to leukapheresis to be eligible to participate in the study:

1. Subject (or legally authorized representative) has voluntarily agreed to participate by giving written Informed Consent/Assent (as applicable) in accordance with International Council for Harmonization (ICH) GCP guidelines and applicable local regulations.
2. Subject (or legally authorized representative) has agreed to abide by all protocol-required procedures including study-related assessments and management by the treating institution for the duration of the study, including the LTFU.
3. Age ≥ 18 years to ≤ 75 years at the time the Pre-screening Informed Consent.
4. Histologically or cytogenetically confirmed diagnosis of advanced (metastatic or inoperable) esophageal or GEJ cancers.
5. Subject has received a maximum of two prior lines of combination or single agent systemic treatment for advanced or metastatic disease before treatment with ADP-A2M4CD8 as the next therapy.
    a. Esophageal or GEJ cancers
    Prior therapy requirements in the unresectable locally advanced or metastatic setting:
        - Subjects should have received a platinum and/or fluoropyrimidine-based regimen (such as FOLFOX).
        - Subjects may have received anti-PD-1 agent in combination with fluoropyrimidine- and platinum-containing chemotherapy or been offered if available.
        - Subjects may have been offered taxane-containing regimen, ramucirumab, and/or irinotecan-containing regimen, if available; unless discussed and agreed upon with the sponsor.
        - Subjects whose tumors are known to be HER2/neu positive should have received or been offered a HER2/neu receptor inhibitor, if available.

b. Esophageal squamous cell carcinoma
Prior therapy requirements in the unresectable locally advanced or metastatic setting:
- Subjects should have received a platinum and/or fluoropyrimidine-based regimen (such as FOLFOX) and may include a taxane-containing regimen, and/or irinotecan-containing regimen.
- Subjects whose tumors express PD-L1 or MSI-H/dMMR tumors, should have received or been offered anti-PD-1/anti-PD-L1 therapy if available; unless discussed and agreed upon with the sponsor

6. Measurable disease according to RECIST v1.1 criteria.
7. Positive for HLA-A*02:01, HLA-A*02:03, or HLA-A*02:06 allele via Adaptimmune-designated central laboratory testing. HLA-A*02 alleles having the same protein sequence in the peptide binding domains (P group) will also be included. Other HLA-A*02 alleles may be eligible after adjudication with the Sponsor. The Sponsor will review the results of HLA typing for inclusion alleles and will adjudicate subject eligibility based on HLA results.
8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥ 2+ staining in ≥ 30% of the cells by IHC. All samples must have been pathologically reviewed by an Adaptimmune-designated central laboratory confirming expression.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
10. Left ventricular ejection fraction (LVEF) ≥ 50% or the institutional lower limit of normal range
11. Fit for leukapheresis and adequate venous access can be established for the cell collection.
12. Female subjects of childbearing potential (FCBP) must have a negative urine or serum pregnancy test AND must agree to use a highly effective method of contraception starting at the first dose of chemotherapy and continuing for at least 12 months or 4 months after the gene modified cells are no longer detected in the blood, whichever is longer.

    OR

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

System	Laboratory Value
Hematology	
ANC	≥ 1.5 x 10^9/L (without granulocyte-colony stimulating factor [G-CSF] support)

Platelets	≥ 100 x 10^9/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Hemoglobin	≥ 90 g/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Coagulation	
Prothrombin Time or International Normalized Ratio	≤ 1.5 x upper limit of normal (ULN) unless receiving therapeutic anticoagulation
Partial Thromboplastin Time (PTT)	≤ 1.5 x ULN unless receiving therapeutic anticoagulation
Renal	
Glomerular Filtration Rate or Creatinine Clearance (CrCl) (Estimated or Calculated)[1]	≥ 50 mL/min
Hepatic	
Serum Total Bilirubin	≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin < 35% of total bilirubin) Exception: Subjects with liver metastasis ≤ 2.5 x ULN
ALT/AST	≤ 2.5 x ULN Exception: Subjects with liver metastasis ≤ 5.0 x ULN
[1]Renal function (GFR) will be estimated or measured according to standard practice at the treating institution. Renal function will be reassessed at Baseline using the same methodology.	

14. Subjects must have ≥ 90% room air oxygen saturation test at rest at Screening (within 7 days of leukapheresis) and at Baseline.

5.3. Exclusion Criteria

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

1. Positive for HLA-A*02:05 in either allele via Adaptimmune-designated central laboratory testing. HLA-A*02 alleles having the same protein sequence as HLA-A*02:05 in the peptide binding domains (P groups) will also be excluded. Other alleles may be exclusionary after adjudication with the Sponsor.
2. Received or plans to receive the following 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

Treatment/Therapy	Required Wash-Out Prior to Leukapheresis	Required Wash-Out Prior to Lymphodepletion
Tyrosine kinase inhibitor (e.g., dabrafenib, trametinib, and vemurafenib)	1 week	1 week
Immune therapy (including monoclonal antibody therapy and checkpoint inhibitors)	2 weeks	4 weeks
Anti-cancer vaccine	8 weeks in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months.	8 weeks in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months.
Gene therapy using an integrating vector	Use of previous gene therapy using a Lentiviral vector is permitted only if transduced T-cells represent less than 1% of peripheral blood mononuclear cells (PBMCs) (< 1500 copies of vectors per microgram of PBMC DNA) at the time of screening. Eligibility testing must be done by Adaptimmune's designated Contract Research Organization (CRO).	Not permitted after leukapheresis and prior to lymphodepletion
Corticosteroids or any other immunosuppressive therapy. Note: Use of topical steroids is not an exclusion. See Section 6.5 for exceptions.	2 weeks	2 weeks

Treatment/Therapy	Required Wash-Out Prior to Leukapheresis	Required Wash-Out Prior to Lymphodepletion
Anti-MAGE-A4 Therapy Note: Fresh screening biopsy post-anti-MAGE-A4 therapy must be obtained to confirm MAGE-A4 positivity.	2 weeks	2 weeks
Investigational treatment or interventional clinical trial	4 weeks	4 weeks
Allogeneic hematopoietic stem cell transplant	Not permitted within any amount of time	Not permitted within any amount of time
Radiotherapy to the target lesions	N/A	3 months. A lesion with unequivocal progression may be considered a target lesion regardless of time from last radiotherapy dose. (Note: There is no wash-out period for palliative radiation to non-target organs).
Major surgery	N/A	4 weeks. Subjects must have recovered from any surgically related toxicities.
Note: Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician.		

3. Toxicity from previous anti-cancer therapy must have recovered to ≤ Grade 1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia and vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g., peripheral neuropathy) can be enrolled.
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide, or other agents used in the study.
5. History of autoimmune or immune-mediated disease. Subjects with hypothyroidism, diabetes, adrenal insufficiency, or pituitary insufficiency that are stable on replacement therapy are eligible. Subjects with disorders such as asthma, psoriasis, or atopic dermatitis that are well controlled without requiring systemic immunosuppression are also eligible.
6. Leptomeningeal disease, carcinomatous meningitis, or symptomatic CNS metastases. Subjects with a prior history of symptomatic CNS metastases must have received treatment (i.e., stereotactic radiosurgery and whole brain radiation or surgery) and be neurologically stable for at least 1 month, not requiring anti-seizure medications and off of steroids for at least 14 days prior to leukapheresis and lymphodepletion. Anti-seizure prophylaxis is

permitted. Subjects who have asymptomatic CNS metastases without associated edema, shift, requirement for steroids, or anti-seizure medications for the treatment of seizures are eligible. REGIONAL REQUIREMENT IN UK: Leptomeningeal disease, carcinomatous meningitis, or symptomatic CNS metastases.

7. Any other prior malignancy that is not in complete remission. Resectable squamous or basal cell carcinoma of the skin is acceptable. Prior malignancies that have been surgically resected and show no evidence of disease are acceptable.
8. Uncontrolled intercurrent illness including, but not limited to:
    - Ongoing or active infection
    - COVID-19 infection or a positive COVID-19 Real-Time Polymerase Chain Reaction RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy. If subject has had a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart
    - Clinically significant pulmonary disease with any one pulmonary function parameter < 60% predicted (FEV1 or TLC or DLCO) assessed prior to leukapheresis and within 2 months of the start of lymphodepleting chemotherapy
    - Requirement for oxygen support (for cardiac or pulmonary disease)
    - Clinically significant cardiac disease defined by congestive heart failure New York Heart Association Class 3 or Class 4
    - Uncontrolled clinically significant arrhythmia
    - Acute Coronary Syndrome (angina or myocardial infarction) in last 6 months
    - Congenital or family history of long QT syndrome or a history of torsade de pointes
    - Current uncontrolled hypertension despite optimal medical therapy
    - History of stroke or CNS bleeding; transient ischemic attack or reversible ischemic neurologic deficit in the last 6 months
9. Active infection with HIV, HBV, HCV, or HTLV as defined below:
    - Positive serology for HIV.
    - Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months.
    - Active hepatitis C infection as demonstrated by hepatitis C RNA test. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT-PCR or branched DNA (bDNA) assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value.
    - Positive serology for HTLV 1 or 2.

- Re-screening for infectious disease markers is not required at Baseline (prior to lymphodepletion) unless > 6 months has elapsed.

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

5.4. Screen Failures

A screen failure log documenting the Investigator's assessment of each screened subject with regard to the protocol inclusion and exclusion criteria is to be maintained by the Investigator. Data on subjects who fail pre-screening or screening, including demographics and disease history, will be collected in the electronic case report form (eCRF) to support companion diagnostic development and validation.

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

5.5. Number of Subjects and Study Duration

Forty-five subjects are planned to be dosed in this study to robustly evaluate clinical benefit/risk in subjects who received the ADP-A2M4CD8 T-cell therapy.

Clinical cut-off for the primary analysis will occur once the last subject dosed has up to 6 months follow-up post-T-cell infusion or has ended the Interventional phase of the study. At this time, all safety and secondary efficacy endpoints will also be summarized to provide supportive evidence to the primary assessment.

The study will be considered complete once all subjects complete 15 years of follow-up or discontinue from the study for any reason.

5.6. Sites

The study will be conducted in approximately 35 sites in North America and Europe. The number of centers is necessary to ensure recruitment in this rare subject population. Additional sites may be added at the discretion of the Sponsor.

6. STUDY INTERVENTION

6.1. Leukapheresis

Subjects who complete screening procedures defined in Section 5.1 and who meet all eligibility criteria defined in Section 5.2 and Section 5.3 will be eligible to undergo leukapheresis to obtain starting material for the manufacture of autologous ADP-A2M4CD8.

At the discretion of the Investigator and to allow for adequate planning for the subjects to be treated in this protocol, leukapheresis can be performed as soon as possible after the subject is determined to be eligible for study participation. Leukapheresis can be performed prior to

initiating second-line treatment regimen or at the end of second-line treatment. For early leukapheresis, subjects should meet all eligibility requirements with the exception of prior anti-cancer therapy.

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

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

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

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

Any remaining subject apheresis material that is not required for further manufacture of ADP-A2M4CD8 may be used by the Sponsor for research to modify or improve the manufacturing process and to enhance the clinical response.

6.2. Lymphodepleting Chemotherapy

Prior to the administration of lymphodepleting chemotherapy, all eligibility criteria will be reconfirmed, baseline tumor assessment will be obtained, and any issues or concerns are addressed in advance of lymphodepletion, in particular, any factor that might cause or increase the risk of prolonged cytopenia. Where issues are identified, the Investigator is encouraged to adopt mitigation measures such as a modified lymphodepleting regimen or alternative treatment options, if appropriate. Once the manufactured ADP-A2M4CD8 product has been received at the clinical site and the integrity of the bag(s) has been verified by the site, eligible subjects will proceed to have lymphodepleting chemotherapy with fludarabine and cyclophosphamide as described in Table 4. Dose justification for the lymphodepletion regimen is described in Section 4.3.

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

On admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis (Section 10.5.3.7) in line with institutional guidelines.

Appropriate IV hydration should be administered, and mesna should be given to prevent urotoxicity while cyclophosphamide is administered, as described 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 from 24 hours after the last dose of lymphodepleting

chemotherapy until resolution of neutropenia in accordance with American Society of Clinical Oncology (ASCO) guidelines or institutional practice (Section 6.2.3).

Table 4: Fludarabine and Cyclophosphamide Treatment Schema

Lymphodepleting Chemotherapy				
Day	**Drug**	**Dose**	**Route**	**Administration** [b]
-7	**Fludarabine**[a]	30 mg/m^2	IV	in 50–100mL 0.9% NaCl over 30 mins
	Cyclophosphamide[c]	600 mg/m^2	IV	in 100–250mL 0.9% NaCl over 1 hour
-6	**Fludarabine**[a]	30 mg/m^2	IV	in 50–100mL 0.9% NaCl over 30 mins
	Cyclophosphamide[c]	600 mg/m^2	IV	in 100–250mL 0.9% NaCl over 1 hour
-5	**Fludarabine**[a]	30 mg/m^2	IV	in 50–100mL 0.9% NaCl over 30 mins
	Cyclophosphamide[c]	600 mg/m^2	IV	in 100–250mL 0.9% NaCl over 1 hour
-4	**Fludarabine**[a, d]	30 mg/m^2	IV	in 50–100mL 0.9% NaCl over 30 mins
1	**ADP-A2M4CD8 infusion**[e]			

[a] Fludarabine dose will be adjusted for renal impairment as described in Section 6.2.1. The Day-4 dose of fludarabine may be delayed or omitted based on mitigation measures agreed with sponsor.
[b] Per institutional standard practice.
[c] Administration of mesna is described in Section 6.2.2.
[d] Begin G-CSF 24 hours after the last dose of lymphodepleting chemotherapy and continue as per Section 6.2.3. Long-acting (pegylated) G-CSF may be given instead of short-acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give 1 dose 24 hours after the last dose of chemotherapy.
[e] Administration of ADP-A2M4CD8 infusion is described in Section 6.2.3.

6.2.1. Fludarabine Dose Adjustment for Renal Impairment

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

Glomerular Filtration Rate (GFR)	Fludarabine Dose
≥ 80 mL/min	30 mg/m^2
50–79 mL/min	20 mg/m^2

6.2.2. Mesna

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

- 120 mg/m^2 (20% cyclophosphamide dose) per day will be administered pre-infusion and then repeated as an IV bolus at 4 hours and 8 hours (giving a total mesna dose of 360 mg/m^2 per day.

6.2.3. G-CSF

The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. G-CSF should be given daily from 24 hours after the last dose of lymphodepleting chemotherapy until resolution of neutropenia in accordance with ASCO guidelines [Smith, 2015] or institutional standard practice. Long-acting (pegylated) G-CSF may be given instead of short-acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give 1 dose 24 hours after the last dose of chemotherapy.

6.3. Investigational Product

6.3.1. 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.

Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3.

6.3.2. T-cell Infusion

On Day 1, the subject will receive thawed ADP-A2M4CD8 by intravenous infusion.

Prior to infusion, 2 clinical personnel in the presence of the subject, will independently verify and confirm that the information on the infusion bag is correctly matched to the subject, as per the Apheresis and T-cell Manual.

The T-cell product must not be thawed until immediately prior to infusion. The cells can be thawed at a set temperature of 37°C using a water bath or equivalent device. Routinely, the cells should be thawed for approximately 3 to 5 minutes. Smaller volumes may take less time to thaw. The infusion bags should be observed during the thaw process to ensure no frozen material or ice remains.

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

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

The infusion should begin within 10 minutes of completing thaw (per bag) and is recommended to be complete 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 the inner infusion bag is damaged or leaking after thawing, the Investigator and Sponsor should be notified, and the cells should not be infused.

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

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

In the event of adverse reaction to the cell infusion, the infusion rate should be reduced, and the reaction managed according to institutional standard procedures. Steroid treatment should be avoided unless medically required. In the event a subject develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia (Section 10.5.1.1).

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

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

Discharge from hospital post-T-cell infusion will be at the discretion of the Investigator. All subjects must be reviewed by the Investigator (or a designated Study Physician) prior to discharge. REGIONAL REQUIREMENTS (UK and France): Subjects will remain hospitalized for observation for at least 10 days post-T-cell infusion, based on regional requirements.

6.4. Preparation/Handling/Storage/Accountability

6.4.1. Packaging and Labelling

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

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

6.4.2. Receipt and Return

IP must be received by a designated person at the site, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated site personnel have access. IP is to be dispensed only in accordance with the protocol.

The Investigator is responsible for keeping accurate records of the IP received from the Sponsor, including the amount dispensed and any unused IP remaining at the conclusion of the study. Contact the Sponsor or designee regarding any questions concerning the IP.

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

6.4.3. Storage and Handling

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

6.4.4. Investigational Product Accountability/Traceability

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

The Investigator must ensure

- Deliveries of IP are correctly received by a responsible person.
- Such deliveries are recorded.
- IP is handled and stored safely and properly as instructed in the Apheresis and T-cell Product Manual.
- IP is only administered to study subjects in accordance with the protocol.
- IP administration is documented. Records must include the identification of the person to whom the IP was administered, date of infusion, start and stop time of infusion, and the amount infused. This record is in addition to any Investigational Product accountability information recorded on the eCRF.
- 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 IP delivered with records of usage and return/destruction. Any discrepancies must be accounted for on the appropriate forms.

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

6.4.5. Alert Cards

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

6.5. Concomitant Medications

6.5.1. Prohibited Concomitant Medications

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

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

It is preferred that subjects do not undergo surgical resection of tumor lesions during the study prior to disease progression as it interferes with the assessment of the efficacy of MAGE A4^{c1032}T. However, surgery or radiotherapy after trial inclusion and prior to disease progression is a protocol deviation, and if a target lesion has been surgically removed or treated with radiotherapy, then the patient's response is not evaluable. Upon progression, the subject will follow the LTFU schedule. Subjects who have surgery for new lesions consistent with PD or to control PD in previously identified lesions will discontinue from the Interventional phase and follow the LTFU schedule.

See Section 5.3 for details of wash-out 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, ICANS (see Section 10.5.6 and Section 10.5.7 for treatment recommendations), or other significant immune-mediated AEs. According to local standard of care or ASCO guidelines, steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the IP (Day -3). Steroid use is permitted for prophylaxis or treatment of contrast dye allergies. Physiological doses of steroids, including stress doses when clinically appropriate, may be administered as replacement therapy in subjects with adrenal insufficiency. Fludrocortisone is permitted. In general, daily prednisone doses of 0.5 mg/kg or lower, or their equivalent for other corticosteroid agents, are acceptable as physiologic replacement provided that the subject continues to meet eligibility criteria (Section 5.2 and Section 5.3). Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

6.5.2. Permitted Concomitant Medications

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

Other treatment that the Investigator considers necessary for a subject's welfare may be administered during the study at the discretion of the Investigator in keeping with community standards of medical care and in adherence to the protocol.

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

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

6.5.2.1. Vaccinations (Including for COVID-19)

Before immunizing a subject at high risk for vaccine-preventable disease, including for SARS CoV-2 (COVID-19), consult an Infectious Disease specialist or a guidance, such as the CDC Clinical Practice Guideline for Vaccination of the Immuno-compromised Host.

The latest COVID-19 vaccination guidelines from NCCN/EBMT/ASTCT should be consulted by the Investigator. Any individual subject queries which cannot be addressed by the latest expert society guidelines relating to the timing of COVID-19 vaccination prior to either apheresis or lymphodepleting chemotherapy, or post ADP-A2M4CD8 cell infusion, should be discussed with the Medical Monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Temporary Study Stoppage

Throughout the conduct of the study, safety data will be reviewed on an ongoing basis by an external DSMB (refer to Section 10.2). If the following events occur, further enrollment to the study will be suspended and the regulatory authorities informed:

- A subject has a positive RCL if the following occurs:
  - Confirmed positive PBMC RCL and no other vector lot is available (refer to Section 10.7.2 and Figure 1)
  - Confirmed biological RCL, all ADP-A2M4CD8 cell infusions are halted (Section 10.7.2 and Figure 1)

Regulatory authorities will be notified of any decisions to halt the study or subject enrollment. 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.

7.2. Ending the Interventional Phase

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

- Disease progression per RECIST v1.1
- Clinical progression
- Death
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- AE
- Lost to follow-up (Section 7.4)
- Pregnancy (Section 8.5.5)
- Termination of the study by the Sponsor

All subjects, with the exception of those who withdraw consent, die, are lost to follow-up or do not receive any T-cells, will continue in LTFU for observation of delayed AEs. AEs in subjects who terminate early for any reason (other than withdrawal of consent or lost to follow-up) will be followed as described in Section 8.5.8.

7.3. Subject Discontinuation

A subject will be considered to have completed the study when he/she has died or been followed for 15 years from time of T-cell infusion. 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 entire duration of the trial. If a subject withdraws, all procedures and assessments listed in the withdrawal visit should be performed, unless performed within the previous 30 days.

Reasons for completion or withdrawal of a subject from the study are:

- Unable/unwilling to comply with study requirements
- AE
- Withdrawal of consent
- Investigator decision
- Lost to follow-up (Section 7.4)
- Termination of the study by the Sponsor

7.4. Lost to Follow-Up

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

8. STUDY ASSESSMENTS AND PROCEDURES

The T&Es are provided in Table 1 for the Interventional phase of the study and in Table 2 for LTFU.

8.1. Background Assessments

8.1.1. Demographics

Demographic data including year of birth, age, sex, race and ethnicity (where permitted by national regulations) will be collected at Prescreening and Screening.

8.1.2. Disease History and Tumor-Specific Mutations

The following information will be collected: primary tumor type, date of initial diagnosis, histology grade, and current stage of disease. Additionally, at Screening, current stage of disease and histological molecular tests will be recorded in the eCRF.

8.2. HLA and MAGE-A4 Tumor Antigen Testing

There is no window for obtaining HLA and MAGE-A4 antigen prior to leukapheresis.

8.2.1. HLA

HLA-genotyping at the allelic level (4-digit) will be conducted on a blood sample by an accredited central laboratory contracted by the Sponsor using an FDA-validated HLA Sequencing System for SBT of HLA.

8.2.2. MAGE-A4 Antigen

Once subjects are identified as having the appropriate HLA allele, an archival tumor sample, or fresh biopsy obtained as standard of care, 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 subject's tumor will be tested for MAGE-A4 antigen expression by IHC using an analytically validated and CLIA-certified Clinical Trial Assay. Testing will be completed at a central laboratory contracted by the Sponsor.

A secondary objective of the study is to collect tumor tissue samples for the development and validation of an IVD assay for the screening of tumor MAGE-A4 expression for regulatory approval. Tumor tissue will be collected, processed, and submitted in accordance with the Laboratory Manual. The tumor tissue will be tested using the CLIA-validated MAGE-A4 Clinical Trial Assay for study eligibility determination. The tumor tissue will then be used for the analytical validation (which includes testing for efficiency, sensitivity, specificity, exclusivity, accuracy, and precision), as well as the clinical validation of an IVD companion diagnostic assay. Since the Clinical Trial Assay used in this study is not the candidate IVD companion diagnostic, a bridging study is required in order to demonstrate that the performance characteristics of the two tests are very similar. The bridging study requires that all of the original clinical trial samples tested for eligibility using the Clinical Trial Assay are retested with

the candidate IVD, including samples from subjects excluded from the trial because they were marker-negative by the Clinical Trial Assay.

Details regarding the collection and processing of the screening biopsy, sample requirements, instructions for sample shipment to the central laboratory for MAGE-A4 IHC analysis, and details of subsequent tumor sample storage for companion diagnostic development are located in the Laboratory Manual.

Details for the development and validation of an IVD assay for the screening of tumor antigen expression for regulatory approval is available in a separate protocol.

8.3. Efficacy Assessments

8.3.1. CT/MRI

Imaging scans of the chest, abdomen, and pelvis should be performed at Baseline, Week 4, Week 8, Week 12, Week 16, and Week 24, and every 2 months ±28 days until confirmed disease progression. The Week 4 scan must occur on or after Day 29. Subsequent scans are to be completed within the visit window permitted in the Main T&E table with the exception of confirmatory scans, which should not be performed earlier than 4 weeks (on or after 28 days) after the criteria for response was first met. As the primary endpoint of the study uses an IRAC, scheduled scans from Week 4 through Week 16 should be at least 28 days apart to ensure compliance with the RECIST v1.1 requirement for confirmation of response. Imaging scans should be performed at the time a subject withdraws from the study.

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

See Section 8.4.10 regarding brain MRI for safety assessment.

Acceptable imaging modalities for this study include the following:

- Diagnostic-quality CT scan with oral and/or IV iodinated contrast of the chest and abdomen/pelvis (CT is the preferred modality for tumor assessments).
- MRI of the abdomen/pelvis acquired before and after gadolinium contrast agent administration and, if contrast enhanced CT is contraindicated for a subject, a non-contrast enhanced CT of the chest.
- MRI of the extremities, if clinically indicated.
- MRI of the brain acquired without and with contrast-enhancement (pre- and post-gadolinium chelate IV) (Section 8.4.10).
- Digital photographs of skin lesions including a ruler for estimating the size of the lesion.

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.

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 4 weeks post-infusion of ADP-A2M4CD8, unless there is unequivocal clinical evidence of deterioration. Therefore, imaging scans should not be performed earlier than 4 weeks post-infusion (on or after 28 days). Responses should be confirmed by repeat imaging scan performed no earlier than 4 weeks (on or after 28 days) after the criteria for response was first met. The minimum duration for BOR = SD is 4 weeks (or 28 days) post-ADP-A2M4CD8 infusion.

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

For the study primary endpoint, a central vendor will be responsible for independent assessment of tumor response according to RECIST v1.1. Review and interpretation of image data will be conducted by an appropriately qualified, trained, and experienced reviewer. A written Imaging Charter will be provided to sites to describe the imaging acquisition protocol and standardized procedure for the transfer of image data to the central vendor. The Imaging Charter will also describe the procedures for CT/MRI data handling after the images have been received by the central vendor from the sites.

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

8.3.2. Survival Data

If a subject dies during the study, the date of death will be recorded. If a subject is unable to attend the site for visit, e.g., due to deteriorating condition or a change of location/country, the subject may be followed remotely to obtain survival information.

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

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

8.4. Safety Assessments

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

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

The Clinical Laboratory Tests in Table 5, Section 10.3, describes the assessments and parameters to be collected and recorded.

Screening Visit (Visit 2) assessments should be completed within 28 days of leukapheresis unless otherwise specified. Information regarding ECHO/MUGA scans, ECG, and infectious disease assays performed as standard of care assessments within 4 weeks prior to Screening (prior to study consent) will be acceptable.

Baseline assessments must be conducted and results obtained within 2 weeks (14 days), prior to T-cell infusion.

8.4.1. Medical History

Relevant medical history will be recorded at Screening (Visit 2).

8.4.2. Physical Examination

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

8.4.3. Prior Anti-Cancer Therapies

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

8.4.4. Prior and Concomitant Medications

Current medications and those for the previous 30 days are to be collected at Screening (Visit 2).

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

8.4.5. ECOG

Performance status will be measured using the ECOG performance scale; see Section 10.9 for guidance. It is recommended, where possible, that a subject's ECOG be assessed by the same person throughout the study. The frequency of the ECOG is specified in Table 1.

8.4.6. Vital Signs

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

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

8.4.7. Weight and Height

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

8.4.8. Pulse Oximetry

Oxygen saturation at rest will be assessed at Screening (within 7 days of leukapheresis) and at Baseline according to Table 1. Oxygen saturation should be measured with room air.

8.4.9. Cardiac Assessments

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

8.4.9.1. ECG

A single ECG is required. Heart rate, rhythm, PR, RR, QRS, and QTc intervals will be recorded.

For Screening (Visit 2), ECGs performed as standard of care within 4 weeks prior the visit are acceptable. The ECG on Day 1 will be taken before T-cell infusion starts.

8.4.9.2. ECHO/MUGA

An ECHO or MUGA scan will be performed at Screening to determine LVEF for eligibility. ECHO/MUGA scans performed as standard of care within 4 weeks prior to Screening (Visit 2) are acceptable. Additional scans will only be performed if clinically indicated. Note: the same method of evaluation must be used consistently for any follow-up scans.

8.4.9.3. Telemetry

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

8.4.9.4. Pulmonary Function Tests

Pulmonary function tests (PFTs) (FEV1 and TLC and DLCO) will be performed at Screening to determine eligibility and within 2 months of the start of lymphodepleting chemotherapy. Additional PFTs will be performed only if clinically indicated.

8.4.10. Brain MRI

An MRI of the brain with contrast will be obtained at Baseline, within 1 month prior to lymphodepletion, for all subjects 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 brain metastases are documented at Baseline, then dedicated CT/MRI scans of brain 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 Baseline, then dedicated brain CNS CT/MRI scans should be performed as clinically indicated (refer to Section 5.3, exclusion criterion 6). REGIONAL REQUIREMENT (UK): Screening brain MRI is required where subjects with leptomeningeal disease, carcinomatous meningitis or CNS metastases are excluded.

8.4.11. Renal Function Assessment (Creatinine Clearance)

Renal function (estimated or measured glomerular filtration rate [GFR]) will be assessed at Screening according to institutional standard practice e.g., by prediction formula such as the Cockcroft Gault equation, modification of diet in renal disease equation, Chronic Kidney Disease Epidemiology Collaboration equation, or by 24-hour urine collection to measure CrCl or by nuclear medicine GFR measurement.

Renal function will be reassessed at Baseline using the same methodology.

8.4.12. Hematology

Section 10.3 describes the parameters to be collected and recorded.

In Years 6 to 15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 10.7.2), then laboratory assessments may be discontinued.

8.4.13. Clinical Chemistry

Section 10.3 describes the parameters to be collected and recorded.

In Years 6 to 15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 10.7.2), then laboratory assessments are discontinued.

8.4.14. Coagulation

Section 10.3 describes the parameters to be collected and recorded.

8.4.15. Thyroid Function Tests

Section 10.3 describes the parameters to be collected and recorded.

8.4.16. Hepatic Safety Assessments

For subjects who experience evidence of hepatic toxicity, increased hepatic monitoring criteria will apply to ensure subject safety and to enable evaluation of liver event etiology (Section 10.3).

8.4.17. Pregnancy Test

Either serum or urine pregnancy tests may be performed. FCBPs must have a negative pregnancy test at Screening and prior to starting lymphodepleting chemotherapy.

8.4.18. Infectious Disease Screening

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

Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT-PCR or bDNA assay. Eligibility will be determined based on a negative screening value (see Section 5.3, exclusion criteria 9).

Section 10.3 describes the parameters to be collected and recorded.

8.4.19. CMV PCR

Subjects will be screened for CMV seropositivity at Screening. If subjects are CMV seropositive at Screening, CMV PCR assessments will continue at Baseline, Day 1, Weeks 2, 4, 6, and 8. 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 PCR at Day 1 and Weeks 2, 4, 6, and 8 (see Section 10.5.3.4 for CMV prophylaxis and blood product screening if positive).

8.4.20. ICE Assessment Tool

The Immune Effector Cell-Associated Encephalopathy (ICE) neurological assessment should be performed from Day 1 (prior to T-cell infusion) through Day 8 while the subject is hospitalized, according to Table 1. The ICE assessment may be discontinued once a subject is discharged from the hospital.

If a subject is thought to have ICANS, the ICE assessment should be used at least twice per day until resolution or stabilization. It can also be used at later visits if indicated (Table 10).

8.4.21. C-Reactive Protein

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

8.4.22. Ferritin

If CRS is suspected, ferritin levels should be measured approximately every other day with CRP.

8.4.23. Persistence (Vector Copies)

PBMC samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects. Persistence of transduced T-cells is also a major biomarker related to clinical response. Therefore, additional PBMC samples will be collected over the first 2 years following infusion (Section 8.6.6).

Samples are required for the following:

- Safety at Baseline and Week 24, Month 12 and then every 6 months until Year 5 and annually from Years 6 to 15.
  - If no gene modified cells are detected for three consecutive assessments and the subject is ≥ 5 years post-infusion (e.g., negative persistence assessments at Year 4, 4.5, and 5), no further monitoring of PBMCs is required for persistence and collection of samples may be discontinued (Section 10.7.2).
  - If at Month 12 or beyond post-infusion, greater than 1% PBMCs test positive for vector sequences, the subject's PBMCs will be evaluated for integration site analysis (Section 10.7.2).
- Research at Days 2, 4, and 8 and Weeks 2, 4, 8, and 12, and subsequently every 2 months (±1 month) until disease progression.

See Table 1 and Table 2.

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

8.4.24. Replication Competent Lentivirus (VSV-G DNA)

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

RCL testing will take place on the subject's PBMCs, which are collected at Baseline and post-infusion at Week 12, Week 24, Month 12, and then annually for 15 years (see Table 1 and Table 2 for scheduling).

If all samples are negative in Year 1, 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 (see Section 10.7.2 for additional information).

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

8.5. Adverse Events and Serious Adverse Events

8.5.1. Time Period for Collecting AE and SAE Information

AEs and SAEs will be collected as follows:

- During the Pre-screening period, only SAEs related to protocol-specified procedures will be collected from the time of the procedure (e.g., blood sampling or tumor biopsy) until 24 hours afterwards for blood sampling, or until 2 weeks post-biopsy.
- From date of signing the Treatment Informed Consent until the day before lymphodepletion starts, only SAEs related to study design/procedures (protocol mandated procedures, invasive tests, or change in existing therapy) or AEs leading to withdrawal from the study will be collected.
- All AEs and SAEs will be collected from the start of lymphodepletion until the subject has discontinued the Interventional phase of the study. In addition, emerging clinical conditions defined in Section 10.4.6 will be monitored starting Day 1. If the subject has not progressed after 12 months, only those emerging clinical condition defined in Section 10.4.6 will be collected thereafter.
- During the LTFU phase of the study, subjects will only be monitored for the emerging clinical conditions (LTFU AEs) defined in Section 10.4.6 and these will be recorded. If a subject enters the LTFU phase prior to Week 12, they will have full AE collection at the Month 2 visit.

All SAEs will be recorded on the SAE worksheet (SAEW) and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Section 10.4.6.

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

8.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of an AE and an SAE, and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

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

8.5.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Section 10.4.3.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt (within 24 hours) notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. These safety reports are forwarded to Investigators along with Investigator Safety Letters (ISL).
- An Investigator who receives an Investigator safety letter describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor will submit detailed records of all adverse events that are reported by the relevant Investigator(s).

8.5.5. Pregnancy

- Pregnancy (or pregnancy of a male subject's partner) is not considered an AE/SAE unless there is reason to believe the pregnancy may be the result of failure of the contraceptive being used due to interaction with the IP. Details of all pregnancies in female participants and female partners of male participants will be collected from the start of lymphodepletion for as long as there is evidence of T-cell persistence, or until the subject has confirmed disease progression.

- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.6.2.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

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

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

The contraception guidelines provided in Section 10.6.1 should continue to be adhered to during LTFU.

A woman who becomes and remains pregnant during the study will be discontinued from the Interventional phase, as exposure to radiation from imaging studies is contraindicated. The subject would follow the LTFU T&E table (Table 2).

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

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 symptoms cannot be determined as exclusively due to progression of the underlying malignancy, or do 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/SAE.

8.5.7. AEs of Special Interest

8.5.7.1. Cytokine Release Syndrome

CRS is a potentially life-threatening toxicity that has been observed following administration of antibodies and adoptive T-cell therapies for cancer. It is defined clinically by symptoms that can mimic infection, including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash, and dyspnea. Subjects should be assessed clinically for CRS at all visits according to Table 1. Most cases of CRS present within 7 days following cell infusion. It is important to evaluate the subject for concurrent infections. Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome,

neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. CRS may also be associated with findings of macrophage activation syndrome or occur coincident with tumor lysis syndrome.

CRS is associated with rapid rise in serum cytokine levels under conditions of immune activation and although cytokines will be assayed serially throughout the study, results of the assays will not be available in real time. Therefore, CRS should be graded and managed with supportive and immunosuppressive interventions according to the severity of symptoms [Lee, 2019].

The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. CRS should be graded and managed with supportive measures and anti-IL-6 according to the severity of symptoms; see Section 10.5.6 for detailed guidance on management of CRS.

8.5.7.2. Immune Effector Cell-Associated Neurotoxicity Syndrome

Neurotoxicity has been described in association with immune effector cell therapy and termed immune effector cell-associated neurotoxicity syndrome, or ICANS [Lee, 2019]. ICANS 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 ICANS (defined as > Grade 2), seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral edema may also occur.

ICANS occurring within the first 5 days after immunotherapy may be concurrent with high fever and CRS symptoms. This form of ICANS tends to be of shorter duration, lower grade (Grades 1 or 2; Table 8) and is generally reversible with anti-IL-6 therapy. ICANS presenting as delayed neurotoxicity with seizures or episodes of confusion can occur three or four weeks after CAR T-cell therapy, after the initial fever and CRS subside [Lee, 2019].

ICANS may occur with other cancer immunotherapies, including TCRs. Cancer subjects 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 ICANS in relation to T-cell therapy.

8.5.7.3. Prolonged Cytopenias

Prolonged cytopenias for ≥ 4 weeks from T-cell therapy, and pancytopenia after initial bone marrow recovery from high-dose chemotherapy followed by infusion of adoptive T-cell therapy with bone marrow failure/aplastic anemia have been reported with T-cell therapies [D'Angelo 2017; KYMRIAH EU SmPC; KYMRIAH USPI; YESCARTA EU SmPC; YESCARTA UPSI].

Subjects may be symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. Blood counts are collected according to Table 1. The 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 prolonged or recurrent cytopenia with aplastic anemia is challenging. Treatment is largely supportive, including transfusions and treatment of infections.

See Section 10.5.8 for management guidance if there is evidence of, or concern for the development of cytopenia (decreasing hemoglobin, platelets or neutrophils, or increasing transfusion requirements) that is either prolonged for ≥ 4 weeks from T-cell therapy or following initial bone marrow recovery.

8.5.8. Long-Term Follow-Up Adverse Events

During the LTFU phase of the study, adverse event collection is limited to: new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, new incidence of a hematologic disorder, opportunistic and/or serious infections, or unanticipated illness and/or hospitalization deemed related to gene modified cell therapy. If a subject enters the LTFU phase prior to Week 12, they will have full AE collection at the Month 2 visit. See Section 10.4.6 for reporting AEs during LTFU.

8.5.8.1. LTFU Letter to Primary Care Physician/Oncologist

A letter should be sent by the Investigator/Study Coordinator to the subject's primary care physician, local oncologist, or other physician that will notify him or her of this research study and will outline the features to look for and report as delayed adverse events potentially related to this study (Section 10.7.4).

8.6. Biomarkers for Exploratory Objectives

Sample types collected and rationale: Collection of samples for biomarker research is part of this study. The following samples for biomarker research are requested and will be collected from all participants in this study as specified in the Time and Events Table 1:

- Tissue
  - Tumor: Efficacy of immunotherapy of cancer is conditioned by the interplay between tumor cells and resident or infiltrating immune cells (effector T-cells and immunosuppressive cells). Therefore, tumor biopsies will be collected to evaluate the evolution of both tumor and immune components pre- and post-infusion.
- Blood
  - Serum: Serum is collected to allow for measurement of cytokines in the blood in relation to T-cell expansion and CRS. Serum samples may also be used to detect other soluble biomarkers such as anti-tumor antibodies.
  - [redacted]

[redacted]

8.6.1. Tumor Biopsy

Baseline biopsy material may be collected anytime within 2 months of the T-cell infusion, with preference for a biopsy to be taken closer to the time of infusion. Tumor tissue should either be

taken from non-target lesions or from target lesions where sampling can be done without impacting lesion measurement.

As a guidance and if possible, a responding lesion should be biopsied at the Week 4 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, or activity).

The Week 4 time point tumor biopsy can be collected anytime between Week 3 and Week 8.

The progression time point tumor biopsy can be obtained post-progression (e.g., from an excisional surgery). Additional details regarding the tumor biopsy collection are provided in the Laboratory Manual.

In subjects who have a pleural effusion or ascites, if there is a clinical requirement for removal of the effusion fluid at any time during the study, collection of samples for Adaptimmune translational research studies are requested, and if possible, all cells recovered in the draw.

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

Clinically obtained pleural effusion/ascites 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. Pleural effusions/ascites fluid collected in this study 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.

8.6.2. Cytokine and Soluble Protein Analysis

Serum is collected at Baseline, pre-infusion and 2 to 4 hours post-infusion on Day 1, Day 2, Day 4, Day 8, Week 2, Week 3 (Day 22), Week 4, Week 8, Week 12, Week 24, and every 2 months post-infusion, 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 Laboratory Manual.

Serum samples may also be used to detect humoral immune responses to tumor antigens and antibodies to ADP-A2M4CD8.

8.6.3. [redacted]

[redacted]

8.6.4. Gene expression analysis in whole blood

RNA sequencing will be performed on whole blood to investigate changes in global gene expression over time. The analysis will include characterization of T-cell and B-cell receptor (BCR) repertoires in blood and tumor tissues at Baseline and after infusion. These studies will support the understanding of TCR/BCR diversity and clonality and how these relate to the trafficking of ADP-A2M4CD8 SPEAR T-cells from peripheral blood to tumor lesions, and their expansion within the tumor microenvironment (TME).

Whole blood collections scheduled at Baseline, Pre-infusion, Week 4, (anytime between Week 3 and Week 8), Week 12 and withdrawal, are to be collected within 24 hours of the corresponding tumor biopsy tissue.

8.6.5. [redacted]

[redacted]

8.6.6. Persistence of ADP-A2M4CD8 Cells

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. Research samples will be taken as detailed in Section 8.4.23. Persistence is also monitored long term as a safety measure (Section 10.7.2). 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]

8.7. Subject-Reported Outcomes

8.7.1. EuroQOL Group EQ-5D 3 Level Version (EQ-5D-3L)

EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal [EuroQOL, 1990]. The EQ-5D is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care. The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The respondent is asked to indicate his/her health state by selecting the most appropriate statement in each of the 5 dimensions. The EQ visual analogue scale records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The EQ-5D-3L will be administered at Baseline and post-T-cell infusion at Week 8, Week 16, Week 24, and at Month 12 if the subject remains in the interventional phase of the study. Once disease progression is established, the EQ-5D-3L assessment is no longer required.

9. STATISTICAL CONSIDERATIONS

The objectives and endpoints for this study are described in Section 3. This section focusses on key aspects of the analysis and reporting of the primary and secondary efficacy and safety endpoints. Details for the analysis of all clinical endpoints will be provided in the statistical analysis plan (SAP). A separate analysis plan will be developed for the exploratory biomarkers.

9.1. Study Populations

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

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

Per-protocol (PP) population: A PP population may be included if there are subjects in the mITT population who have protocol violations that are expected to affect efficacy assessments (e.g., subjects enrolled who do not meet key eligibility criteria) during the trial. Protocol violators resulting in exclusion from the PP population will be identified and documented prior to database lock.

The primary analysis will occur at the time of clinical cut-off as described in Section 5.5.

9.2. Statistical Hypotheses and Sample Size Assumptions

The primary objective for this study is to evaluate the efficacy of autologous genetically modified T-cells (ADP-A2M4CD8).

The primary endpoint for efficacy is ORR defined as the proportion of subjects with a confirmed complete response (CR) or confirmed partial response (PR) relative to the total number of subjects in the analysis population.

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

Subjects with an unknown or missing response will be treated as non-responders (i.e., they will be included in the denominator when calculating the proportion).

The clinical and statistical assumptions, the hypothesis test, and the sample size for the proposed clinical trial are based on the following factors:

- As stated in Section 2.2.3, clinical evidence indicates the historical ORR for therapies administered to subjects who progressed on or after at least 2 prior systemic therapies for esophageal and GEJ cancers is 14%.
- The ORR for the historical control that will be used for hypothesis testing in this study will be 14%.
- The mechanism of action for the TCR is assumed to be the same for adenocarcinoma and squamous cell carcinoma.
- As stated in Section 2.1.1, 1 of 2 subjects with GEJ cancers treated with ADP-A2M4CD8 cells had a PR in the ADP-0055-001 SURPASS phase 1 study. In that same study, 4 additional subjects with other tumor types were treated, with 1 such subject also having a PR. All other subjects had best overall response of stable disease. Because of this preliminary evidence, for purposes of sample size computation, we assumed ORR for ADP-A2M4CD8 cell therapy would be 35% (Section 2.3.1).

The hypothesis of interest for the primary endpoint is:

Null Hypothesis (H_0): $p \leq p_0$ vs. Alternative Hypothesis (H_1): $p > p_0$, where p_0 (historical ORR) = 0.14.

Statistical design assumptions:

- The assessment for efficacy will be based on the mITT population using confirmed ORR via RECIST v1.1 by the IRAC.
- The type I error (α) for this test will be no more than 0.049.
- The type II error (β) will not exceed 0.1.
- Exact binomial methods will be used to test the hypothesis.

According to a Chen's three-stage design, approximately 45 subjects will be enrolled.

- First Stage: 15 evaluable subjects will be enrolled in stage 1. The predefined ORR is met if there are 2 or more confirmed complete response (CR) or confirmed partial response (PR) out of the first 15 evaluable subjects based on investigator radiological assessment.

  Subject enrollment will continue to the next stage if there is a demonstrable clinical benefit from treatment with cell therapy and there are no major safety concerns. Otherwise, subject enrollment will be stopped. The independent DSMB will make this recommendation.

  The DSMB will review safety data (including AEs and SAEs), ongoing efficacy data for futility, and overall benefit:risk profile, and make a recommendation to Adaptimmune. The process for the review will be defined in the DSMB charter.
- Second Stage: An additional 13 evaluable subjects will be enrolled in stage 2, if the predefined ORR is met (i.e., 7 or more responses, confirmed CR or confirmed PR, out of the first 28 (15 + 13) evaluable subjects based on investigator radiological assessment), then the study will continue to the third and final stage.

  Subject enrollment will continue to the next stage if there is a demonstrable benefit from treatment with cell therapy and there are no major safety concerns. Otherwise, subject enrollment will be stopped. The independent DSMB will make this recommendation.
- Third Stage: An additional 17 evaluable subjects will be enrolled for a total of 45 (15 + 13 +17) evaluable subjects.

9.3. Statistical Analyses

The SAP document will provide full details about analysis methods, data derivations, and displays. This section captures key aspects of the analysis.

Demography and baseline characteristics will be summarized using appropriate descriptive statistics. Subject disposition, including the number of subjects leukapheresed, lymphodepleted, and treated with ADP-A2M4CD8, will be summarized. Reasons for subject discontinuation from the study will be displayed. Other subgroups, such as region, may be explored, and these will be discussed in the SAP.

9.3.1. Interim Analysis

Interim analysis will be performed according to Chen's three stage design based on the mITT population as described in Section 9.2.

9.3.2. Efficacy Anti-Tumor Activity Analyses

The primary analysis population for efficacy will be the mITT population. Secondary analyses may be conducted on the ITT and PP populations if they are different from the mITT population.

The primary endpoint, ORR will be based on confirmed (tumor) responses per RECIST v1.1 by the IRAC. The ORR will be summarized using Clopper-Pearson (exact binomial) 2-sided 95% CIs.

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

As a sensitivity analysis, 2-sided 95% confidence intervals using the Wilson method may also be provided.

The following secondary efficacy endpoints will be summarized:

- Time to confirmed response, defined as the duration between T-cell infusion and the initial date of the confirmed response, by primarily the IRAC and secondarily the investigator radiological assessment.
- DoR, defined as the duration between the initial date of the confirmed response to the date of PD or death, where tumor response and disease progression are evaluated by primarily the IRAC and secondarily the investigator radiological assessment.
- BOR, defined as the best response recorded from the date of T-cell infusion until disease progression. Response categories from best to worse are: confirmed CR, confirmed PR, SD, PD, and NE (per RECIST v1.1 by primarily the IRAC and secondarily the investigator radiological assessment).
- PFS, defined as the duration between the date T-cell infusion and the earliest date of disease progression based on RECIST v1.1 (by primarily the IRAC and secondarily the investigator radiological assessment) or death due to any cause.
  - Since subjects are expected to progress in the Interventional phase (see Section 4.4) before entering LTFU, 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 LTFU (see Section 4.2.4), the death date will be captured from LTFU to summarize PFS.
- OS, defined as the duration between T-cell infusion and death.

Independent assessment of progression based on RECIST v1.1 will be used for the primary analysis of TTR, DoR, BOR, and PFS. Investigator assessment of progression based on RECIST v1.1 will be used for the secondary analysis of TTR, DoR, BOR, and PFS. As a sensitivity analysis, determination of progression (via RECIST v1.1) using lesion assessments will also be provided.

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

Detailed censoring rules for all time-to-event endpoints will be specified in the SAP. The proportion of censored observations will be summarized.

The surrogates of treatment effect will be described by summaries of peak expansion (i.e., maximum persistence) and time to peak expansion by responder status and overall. Persistence data will also be displayed by subject line plots.

The exploratory endpoint of EQ-5D-3L will be summarized using appropriate summary statistics, by time, responder status, and overall.

9.3.3. Safety Analyses

The primary analysis population for safety will be the mITT population. Safety will also be summarized for the ITT population and may include the per protocol (PP) population.

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

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

AEs will be summarized using three time periods:

- From the time of signing the Treatment ICF
- From start of lymphodepleting chemotherapy, defined as starting on the first day of lymphodepleting chemotherapy through the end of interventional phase
- From the end of interventional phase until up to 15 years after the last T-cell infusion

AEs throughout the trial will be coded by MedDRA v 23.0 or higher. The number and percentage of subjects reporting any AEs will be tabulated by system organ class and preferred term. AEs will be further classified by toxicity grade, relationship to treatment, and seriousness in tabulation.

Summary data on duration, grade, time to onset for adverse events of special interest (i.e. CRS, ICANS) will be presented. Data from ICE will be listed.

For subjects in the LTFU phase, the LTFU AE will be summarized and listed.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Data Handling and Record Keeping

10.1.1.1. Data Management

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

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

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

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

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

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

10.1.1.2. Case Report Forms

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

10.1.1.3. Site Documentation and Source Data

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

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

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

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

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

10.1.1.4. Data Retention and Availability

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

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

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

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

10.1.2. Study Monitoring

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

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

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

10.1.2.1. Audits and Inspections

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

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

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

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

10.1.3. Regulatory and Ethical Considerations

10.1.3.1. Competent Authority Submissions

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

10.1.3.2. Independent Ethics Committees

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

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

10.1.3.3. Local Regulations/Declaration of Helsinki

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

10.1.4. Informed Consent

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

should be translated and communicated to the subject in a language that is understandable to the subject. Certified translations of the Informed Consent documentation will be provided as applicable.

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

Tests performed as standard of care prior to documentation of consent may be used for screening results as appropriate (Section 8.4).

10.1.5. Confidentiality

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

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

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

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

10.1.6. Protocol Adherence

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

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

10.1.7. Study Suspension, Study Termination, and Study Completion

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

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

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

10.1.8. Public Posting of Study Information

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

10.1.9. Clinical Study Report

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

10.1.10. Publication Policy

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

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

10.1.11. Financial Disclosure

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

10.2. Appendix 2: Safety Review

10.2.1. Data Safety Monitoring Board

An external, independent DSMB will be implemented for this study and will consist of two experienced oncologists who are independent of the study and an independent statistician.

The DSMB will review ongoing safety (including AEs and SAEs) during the Interventional phase of the study as outlined in the DSMB charter. The DSMB will review safety data (including AEs and SAEs), ongoing efficacy data for futility, and overall benefit:risk profile.

A DSMB charter, defining roles and accountabilities and the process for review, will be available prior to the start of the study.

10.3. Appendix 3: Clinical Laboratory Tests

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

Table 5: Protocol-Required Safety Laboratory Assessments

Hematology:	Red blood cell count Hemoglobin Hematocrit Mean cell volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Reticulocytes Platelet count White blood cell count with differential (absolute or percentage) • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical Chemistry:	Calcium Phosphorus Magnesium Albumin Bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Lactate dehydrogenase (LDH) Sodium Potassium Bicarbonate/CO_2 Creatinine* Chloride Glucose Blood urea nitrogen or urea * 24 hr urine test or GFR per institutional standards
Other Tests:	Ferritin C-reactive protein (CRP)

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

[1]Not included in infectious disease screening panel. Tested at timepoints in Schedule of Assessments for patients who are CMV seropositive at Screening.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.4.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) ≥ CTCAE Grade 3 and Grade 1 and 2 laboratory abnormalities that the Investigator considers clinically significant in their medical and scientific judgment. • Any other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. A pre-existing condition is one that is present at the start of the study during Screening and is documented in the subject's medical history. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Additional protocol-defined criteria

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

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

AE and SAE Recording

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

Assessment of Severity

Adverse events except for CRS and ICANS will be graded according to the NCI CTCAE v 5.0. See Section 10.5.6 and Section 10.5.7 for guidance on grading of CRS and ICANS, respectively. For AEs not specifically listed in the CTCAE, the Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[1]
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]

- Grade 4 - Life-threatening consequences; urgent intervention indicated
- Grade 5 - Death related to AE

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

[1] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial SAEW report to Adaptimmune. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAEW to Adaptimmune.**
- The Investigator will also assess the relationship between the lymphodepletion chemotherapy and each SAE.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Adaptimmune to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Adaptimmune with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- SAE follow-up information should be submitted on an updated SAEW within 24 hours if associated with a change in diagnosis and/or increased severity. Otherwise follow-up should be submitted promptly within 7 days, and no later than 30 days of receiving new information.

10.4.4. Reporting of SAEs

SAE Reporting to Adaptimmune

- SAEs must be reported to Adaptimmune by completing the paper SAEW within 24 hours of the study personnel's discovery of the event.
- Complete the SAEW as fully as possible and obtain the Investigator's 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.

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

10.4.5. Hepatic Monitoring and Follow-Up Assessments

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

If a Subject meets one of the criteria defined in Table 6, the specified actions and follow-up assessments will be carried out.

If a Subject moves to the LTFU phase prior to Week 12, all AEs would be collected at the Month 2 visit (Section 1.3). Hepatic safety assessments will be included in this safety follow-up.

Table 6: Hepatic Monitoring Criteria

Hepatic Monitoring Criteria	
ALT-absolute	ALT ≥ 8 x ULN
ALT Increase	ALT ≥ 5 x ULN but < 8 x ULN persists for ≥ 2 weeks ALT ≥ 3 x ULN but < 5 x ULN persists for ≥ 4 weeks
Bilirubin[1]	ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN (> 35% direct bilirubin)
International Normalized Ratio (INR)[1]	ALT ≥ 3 x ULN **and** INR > 1.5, if INR measured
Symptomatic[2]	ALT ≥3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions and Follow-Up Assessments	
Actions	**Follow-Up Assessments**
• Complete the eCRF, and an SAEW if the event meets the criteria for an SAE within 24 hours.[1] • Consider hepatologist consultation • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, and bilirubin) and INR. • Perform Follow-Up Assessments (See column to the right) • Monitor participants weekly with liver chemistry and INR until liver chemistry abnormalities resolve, stabilize, or return to baseline. For bilirubin or INR criteria, monitor participant twice weekly. • Fractionate bilirubin if total bilirubin ≥ 2 x ULN.	• Viral hepatitis serology[3] • Serum creatinine phosphokinase and LDH • Complete blood count (CBC) with differential to assess eosinophilia • PBMC blood sample for persistence[4] • Assess for the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity • Record use of concomitant medications (including acetaminophen, herbal remedies, and other OTC medications) and alcohol use • **For bilirubin or INR criteria:** • Hepatologist consultation required • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Liver imaging (ultrasound, MRI, or CT) • Consider liver biopsy

[1] All events of ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT ≥ 3 x ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.

[2] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

[3] Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; CMV IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[4] Record the date/time of the PBMC blood sample draw on the eCRF. Instructions for sample handling and shipping are in the Laboratory Manual.

10.4.6. Reporting Criteria During Long-Term Follow-Up (Years 1-15)

Due to the nature of the treatment, subjects are required to be followed for 15 years after treatment with genetically modified T-cells according to FDA and EMA guidance [FDA, 2020a; FDA, 2010; EMA, 2009]. Subjects will be followed according to the schedule outlined in Table 2. Emergence of any of the following new clinical conditions reported or observed and the action taken will be reported to the Sponsor:

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

These are the only adverse events that will be collected during LTFU.

A detailed description of the event should include the date of diagnosis and the nature of the diagnosis. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites. If a new malignancy is recorded in a vector target T-cell type, tumor cells will be evaluated for vector sequences. If the tumor is positive for vector sequences or the surrogate sample is positive for vector sequences and is confirmed in accordance with 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 investigational new drug applications (INDs) listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment.

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

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

In accordance with FDA and EMA guidance [FDA, 2018; EMA, 2009], all subjects enrolled in this trial are asked to consider an autopsy and autopsies will be requested of the families for all subjects who die during participation in studies after administration of gene transfer agents.

Guidelines for autopsy tissue/sample collection, preparation and shipping are provided in the Laboratory Manual.

10.5. Appendix 5: 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. Staff treating trial subjects should be experienced in acute post-transplant care and the management of associated toxicities (e.g., cytopenias, CRS, ICANS).

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

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

10.5.1. Lymphodepleting Chemotherapy Symptom Management

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

10.5.1.1. Management of Neutropenia

The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF (i.e., filgrastim) should be used in all subjects. G-CSF should be used for management of neutropenia according to ASCO guidelines [Smith, 2015]. G-CSF should be given 24 hours after the last dose of chemotherapy until resolution of neutropenia (reaching an ANC of at least 2×10^9/L to 3×10^9/L or as per ASCO guidelines [Smith, 2015] or per Institutional practice).

Long-acting (pegylated) G-CSF may be given in preference to short acting daily G-CSF in accordance with Institutional standard practice. Pegylated G-CSF will be given as one dose 24 hours after the last dose of chemotherapy.

10.5.2. T-cell Infusion Symptom Management

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

- Fever, chills, headache, and temperature elevations will be managed with acetaminophen. It is recommended all subjects that 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 intravenous fluid administration and further measures as dictated by standard medical practice.
- Hypoxemia will initially be managed with supplemental oxygen and further measures as dictated by standard medical practice.

10.5.3. Infection

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

10.5.3.1. SARS-CoV-2 (COVID-19)

Subjects with a positive RT-PCR test for COVID-19 (irrespective of vaccination status) post lymphodepleting chemotherapy or ADP-A2M4CD8 cell infusion should be immediately referred to an infectious disease specialist for consideration of anti-viral therapies. Investigators should also consult the latest guidelines/institutional policies pertaining to the management of COVID-19 in cancer/cell therapy patients. The Medical Monitor should be informed if a subject has a positive COVID-19 test (irrespective of symptoms) after receiving either lymphodepleting chemotherapy or ADP-A2M4CD8 cell infusion.

10.5.3.2. Pneumocystis jiroveci Pneumonia

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

10.5.3.3. Herpes Simplex and Varicella Zoster

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

10.5.3.4. Cytomegalovirus (CMV)

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

If a subject experiences prolonged or secondary pancytopenia or lymphopenia, additional monitoring for viral reactivation should be considered and treatment for viral infection initiated, if necessary. A strategy for management of pancytopenia or bone marrow failure is described in Section 10.5.8.

10.5.3.5. 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 (300 mg daily), entecavir (0.5 mg daily), or tenofovir (300 mg daily).

10.5.3.6. Syphilis

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

10.5.3.7. Other Anti-Microbial Prophylaxis

Antibacterial and anti-fungal prophylaxis should follow Institutional standards for autologous bone marrow transplants.

10.5.4. 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 Institutional practice) and as clinically indicated. See AABB Guideline on platelet transfusion [Kaufman, 2015].

10.5.4.1. Irradiated Blood Product

The guidance for autologous stem cells is also recommended for use in T-cell therapy.

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

- 7 days prior to and during leukapheresis to prevent the collection of viable allogenic T lymphocytes,

- Irradiated blood components should continue to be used until 3 months following T-cell infusion unless conditioning, disease or previous treatment determine indefinite duration.

Irradiated blood products may be used longer as clinically indicated, otherwise follow institutional guidelines on autologous stem cell transplantation.

10.5.4.2. CMV screened Blood Products

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

10.5.5. Management of Autoimmunity

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

10.5.6. Management of Cytokine Release Syndrome

Table 7 provides the recommended grading of CRS according to grade, which has been further adapted from CTCAE for use with immune effector cell therapy [Lee, 2019] and should be implemented in accordance with Institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels (as described in Section 8.5.7.1) and CRP levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 7: ASTCT CRS Consensus Grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[2]				
Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring high-flow nasal cannula[3], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., continuous positive airway pressure and bilevel positive airway pressure, intubation, and mechanical ventilation)

[Lee, 2019]

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[1] Fever is defined as temperature ≥ 38°C not attributable to any other cause. Inpatients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[3] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

Management guidelines for CRS are provided in Table 8 below:

Table 8: Management Guidelines for CRS

Grade	Management Guidelines
1	**Fever** • Vigilant supportive care including acetaminophen and hypothermia blanket for the treatment of fever. Ibuprofen can be used as second treatment option for fever, if not contraindicated • Assess for infection using blood and urine cultures, and chest radiography[1] • Empiric broad-spectrum antibiotics if neutropenic or otherwise indicated • Maintenance intravenous (IV) fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Initiate tocilizumab 8 mg/kg[3] IV in patients at high risk[2], or if CRS lasts ⩾ 24 hours • If fever persists for ⩾ 8 hours after tocilizumab, or chest imaging demonstrates evidence of pneumonitis or tumor flare, initiate methylprednisolone 1 mg/kg IV daily for 3 days
2	**Hypotension** • IV fluid bolus of 500–1,000 ml of normal saline. Can give a second IV fluid bolus if systolic blood pressure (SBP) remains <90 mmHg • Tocilizumab 8 mg/kg[3] IV for the treatment of hypotension that is refractory to fluid boluses; tocilizumab can be repeated if clinically indicated • If hypotension persists after two fluid boluses and tocilizumab, start vasopressors, consider transfer to intensive-care unit (ICU), obtain echocardiogram, and initiate other methods of hemodynamic monitoring • In patients at high-risk[2] or if hypotension persists requiring a second dose of tocilizumab, dexamethasone should be used at 10 mg IV every 6 h or methylprednisolone equivalent • Manage fever and constitutional symptoms as indicated for grade 1 CRS **Hypoxia** • Supplemental oxygen • Tocilizumab ± corticosteroids and supportive care, as indicated for the management of hypotension **Organ Toxicity** • Symptomatic management of organ toxicities, as per standard guidelines • Tocilizumab ± corticosteroids and supportive care, as indicated for hypotension

Grade	Management Guidelines
3	**Hypotension** • IV fluid boluses as needed, as recommended for the treatment of grade 2 CRS • Tocilizumab as recommended for grade 2 CRS, if not administered previously • Vasopressors as needed • Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring as in the management of grade 2 CRS • Dexamethasone 10 mg IV every 6 h; if refractory, increase to 20 mg IV every 6 h, or methylprednisolone equivalent • Manage fever and constitutional symptoms as indicated for grade 1 CRS **Hypoxia** • Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab plus corticosteroids and supportive care, as indicated for the management of hypotension **Organ Toxicity** • Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab plus corticosteroids and supportive care, as indicated for the management of hypotension
4	**Hypotension** • IV fluids, tocilizumab, vasopressors, and haemodynamic monitoring as defined for the management of grade 3 CRS • Methylprednisolone 1 g/day IV • Manage fever and constitutional symptoms as in grade 1 CRS **Hypoxia** • Mechanical ventilation • Tocilizumab plus corticosteroids and supportive care, as recommended for the management of hypotension **Organ Toxicity** • Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab plus corticosteroids and supportive care, as recommended for the management of hypotension

[1] Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of anti-microbial agents for concurrent bacterial infections.
[2] High-risk defined as high tumor burden (SD >100 mm), bilateral pulmonary tumor involvement, age ≥ 60 years, or other significant comorbidities, such as moderate underlying lung disease, as identified by the Investigator
[3] For subjects requiring intervention beyond supportive measures tocilizumab 8 mg/kg IV should be the first line treatment. Siltuximab 11 mg/kg IV may be used instead of tocilizumab, if unavailable. The maximum dose for tocilizumab is 800 mg per dose. Repeat doses should be given according to tocilizumab prescribing information.
Source: Lee, 2019; Neelapu, 2018

In addition to the above guidelines, consider holding G-CSF during CRS. GM-CSF should be avoided during CRS [Maus, 2020].

Refer to Section 10.5.7.1 below for subjects experiencing Immune Effector Cell-Associated Neurotoxicity Syndrome concurrent with CRS.

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.

Please review the most recent version of the product label for tocilizumab.

10.5.7. Grading and Management of Neurotoxicity

10.5.7.1. Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

The American Society for Transplantation and Cellular Therapy (ASTCT) have developed a grading system for ICANS that incorporates the ICE 10-point neurological assessment (Lee, 2019) tool (Table 9). Points are assigned for each of the tasks in Table 9 that are performed correctly. Normal cognitive function is defined by an overall score of 10. The ICE assessment should be used to monitor all subjects for ICANS.

The ICE assessment used for grading ICANS is presented in Table 9.

Table 9: ICE 10-Point Neurological Assessment (ICE) [Based on Lee, 2019]

Task	ICE Assessment Points
Orientation: Orientation to year, month, city, and hospital	Total of 4 points (1 point for each)
Naming: ability to name 3 objects (e.g., point to clock, pen, button)	Total of 3 points (1 point for each)
Following commands: ability to follow simple commands (e.g., “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1 point
Writing: ability to write a standard sentence, e.g., ‘There are seven days in a week’	1 point
Attention: ability to count backwards from 100 by tens	1 point

The ICE assessment score is used in grading of ICANS as presented in Table 10.

Table 10: Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) [Based on Lee, 2019]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Assessment Score[1]	7–9	3–6	0–2	0 (subject is unarousable and unable to perform ICE assessment)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizures	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on electroencephalography (EEG) that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[3]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intercranial pressure (ICP)/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[4]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE assessment score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a subject with an ICE assessment score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
[1] A subject with an ICE assessment score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE assessment score of 0 may be classified as grade 4 ICANS if unarousable.
[2] Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).
[3] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
[4] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

10.5.7.2. Management of ICANS

Brain MRI (or CT scan if MRI is not feasible) is required at Baseline for all subjects. Baseline brain MRI should be repeated if more than 4 weeks have elapsed prior to lymphodepletion.

The ICE 10-point neurological assessment tool is used to assess neurologic function to monitor for ICANS (Section 10.5.5). The ICE assessment can be administered by a study physician or other healthcare professional. The ICE assessment should be measured on the day of ADP-

A2M4CD8 infusion prior to receiving treatment and through Day 8 while the subject is hospitalized. If the subject is discharged before Day 8, the ICE assessment may be discontinued according to the Main T&E table (Table 1). Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following ADP-A2M4CD8 infusion if hospitalized. If a subject is found to have ICANS, the ICE assessment should be used at every visit (at least twice per day if hospitalized) until resolution or stable. It can also be used at later visits if indicated. The ICE assessments forms part of the grading system for ICANS developed by Lee et al [Lee, 2019].

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

Grade 1 ICANS is primarily managed with supportive care as outlined below. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first-line treatment of for ICANS in the setting of CRS (see Section 10.5.6 for CRS diagnosis and treatment guidelines). In the setting of concurrent CRS, for Grades 1-3 ICANS 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.

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

Table 11: Management of ICANS

Grade	Treatment
1	For all subjects: • Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired • Avoid medications that cause CNS depression • Evaluate for other contributing causes and treat accordingly Unless symptoms are mild and transient (e.g. 1-point change in ICE assessment for less than 12 hours): • Neurology consultation including funduscopic exam to assess for papilledema • MRI of the brain with and without contrast (CT scan of the brain if MRI is not feasible). Further testing if indicated such as diagnostic lumbar puncture with measurement of opening pressure if increased ICP is suspected, or MRI spine if the subject has focal peripheral neurological deficits • Institute levetiracetam therapy and consider EEG if seizure activity is suspected • Consider anti-IL-6 therapy with tocilizumab 8 mg/kg[1] IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent CRS

Grade	Treatment
2	• Supportive care and neurological work-up as described for Grade 1 ICANS • Anti-IL-6 therapy if associated with concurrent CRS • If refractory to anti-IL6 therapy or no evidence of CRS consider Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h; Once initiated continue corticosteroids until improvement to Grade 1 ICANS and then taper • Consider transferring subject to intensive-care unit (ICU) if ICANS associated with Grade ≥ 2 CRS
3	• Supportive care and neurological work-up as indicated for Grade 1 ICANS • ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS if not administered previously • Corticosteroids as outlined for Grade 2 ICANS if symptoms worsen despite anti-IL-6 therapy, or for ICANS without concurrent CRS; continue corticosteroids until improvement to Grade 1 ICANS and then taper • Stage 1 or 2 papilledema with cerebrospinal fluid opening pressure < 20 mmHg should be treated with a corticosteroid regimen as per Grade 4 below. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if subject has persistent Grade ≥ 3 ICANS
4	• Supportive care and neurological work-up as indicated for Grade 1 ICANS • Consider neurosurgical consultation for subjects with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 ICANS • High-dose corticosteroids continued until improvement to Grade 1 ICANS and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days

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

10.5.8. Prolonged Cytopenias

10.5.8.1. Definition of Prolonged Cytopenias, Pancytopenia and Aplastic Anemia

Prolonged cytopenias are defined as Grade 3 or higher neutropenia, anemia, or thrombocytopenia persisting for ≥ 4 weeks from receiving T-cell therapy.

The definition of Grade 3 or higher cytopenia is based on CTCAE criteria (Version 5.0) and is summarized in the table below:

Hgb (g/dL)	Hgb<8.0 g/dL
White blood cell decreased (K/µL)	<2000 mm^3, <2.0 x 10^9/L
Neutrophil count (K/µL)	<1000/mm^3; <1.0 x 10^9/L

Platelet decreased (K/µL)	<50,000/mm^3; <50.0 x 10^9/L

There have been previous reported cases of prolonged cytopenias with lymphodepletion regimens prior to other adoptive T cell therapies [KYMRIAH USPI; KYMIRAH EU SmPC; YESCARTA USPI; YESCARTA EU SmPC]. Cases of aplastic anemia have also been observed after high dose lymphodepletion regimens [D'Angelo, 2017, Chodon, 2014, Nguyen, 2019].

Pancytopenia refers to an abnormal reduction in the number of red blood cells, white blood cells, and blood platelets. Aplastic Anemia is a rare hematological disorder and is defined as diagnosis of severe aplastic anemia made in the setting of 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, with the exclusion of myelodysplastic syndrome.

10.5.8.2. Management of Prolonged Cytopenias

Management of bone marrow suppression and related prolonged cytopenias 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 prolonged cytopenias (decreasing hemoglobin, platelets or neutrophils, or increasing transfusion requirements) persisting for ≥ 4 weeks from T cell therapy, the following measures should be implemented:

1. Consult a physician with expertise in the management of bone marrow suppression.
2. Increase the frequency of CBCs as clinically indicated.
3. Exclude other alternative etiologies such as other drugs, viral causes, etc.
4. An early bone marrow biopsy is recommended for clinical diagnosis, with a sample to be provided to the Sponsor for study. Details on tissue collections, kit use, and shipment information can be found in the Laboratory Manual.
5. A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the Sponsor.
6. Initiate treatment with G-CSF.
7. Consult an Infectious Diseases expert.
8. Once alternative etiologies have been excluded, strongly consider immunosuppression (e.g. methylprednisolone 2 mg/kg initial dose) or more aggressive regimens (e.g. antithymocyte globulin, cyclosporine, eltrombopag) as well as anti-microbial prophylaxis/therapy with the advice of your Hematology/Infectious Diseases consultant(s). If high dose corticosteroids are initiated, duration of therapy and gradual taper should be determined with advice from expert consultants.

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Females of Childbearing Potential (FCBP)

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

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

Women in the following categories are not considered FCBP:

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

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

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6.1. Contraception Guidance

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

- FCBPs 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 be surgically sterile or agree to use a double barrier contraception method or abstain from heterosexual activity with a female of childbearing potential starting at the first dose of chemotherapy and for 4 months thereafter or longer (if indicated in the country specific monograph/label for cyclophosphamide)

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

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

The contraception guidelines should continue to be followed during LTFU.

10.6.2. Collection of Pregnancy Information

10.6.2.1. Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 10.4.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will be discontinued from further efficacy assessments (exposure to radiation from imaging studies is contraindicated in pregnancy) and will follow the LTFU schedule.

10.6.2.2. Male Participants with Partners Who Become Pregnant

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

10.7. Appendix 7: Long-Term Follow-Up

10.7.1. Background to Safety Monitoring in LTFU

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

RCL is a theoretical risk associated with the use of Lentiviral vectors; no RCL has ever been detected *in vitro* or *in vivo*. The risk is derived from the detection of replication competent retrovirus (RCR) during the use of early γ-retroviral vector packaging systems, which were inadequately designed to avoid recombination events between the vector and packaging components [Miller, 1990]. RCR resulted in death due to the onset of lymphoma in 3 of 10 monkeys after receiving bone marrow cells transduced with an RCR contaminated vector lot [Donahue, 1992]. Updated γ-retroviral packaging systems have not been associated with RCR, however as a result of the Donahue study, RCR/RCL must continue to be rigorously evaluated in vector and cell lots, and in subjects post-infusion with any product involving a retrovirus [FDA, 2020a; 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]. A RCL resulting from the production phase of the Lentivirus used in this trial is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Nevertheless, generation of an RCL by recombination with an endogenous virus (i.e., HIV) in the subject following infusion of the cell product remains a theoretical possibility. The consequences of such recombination events could be neutral, could reduce the replication rate or pathogenicity of the subject's endogenous virus, or could increase the replication rate or pathogenicity of the subject's endogenous virus. Since the development of a strain with increased pathogenicity would pose greater risk to both the subject and their close contact(s), periodic monitoring for RCL is conducted during the course of the trial and during the 15-year follow-up.

10.7.1.2. Insertional Oncogenesis

Monitoring for IO follows the recommendations set forth in the FDA and EMA guidance's [FDA, 2020a; FDA, 2020b; EMA, 2009]. IO 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 treated with retrovirus transduced stem cells were found to have insertion near the LIM domain only 2 (LMO2) proto-oncogene promoter, leading to aberrant transcription and expression of LMO2 which resulted in acute T-cell lymphoblastic leukemia [Hacien-Bey-Abina, 2003; Hacien-Bey-Abina, 2014]. Additionally, two subjects treated for X-linked chronic granulomatous disease 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].

10.7.2. Testing for RCL and Persistence

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

If all samples are negative in year one, PBMC samples will be collected and archived annually until 15 years post-infusion. Samples will be archived at the Sponsor's centralized biorepository.

If a positive VSV-G DNA signal is obtained, the Study Investigator will be informed and the subject will be scheduled for a retest as soon as possible and no later than one month after the initial positive result is reported to the Sponsor. The DSMB and the Safety Governance Board will be notified.

Response to potential outcomes of second test:

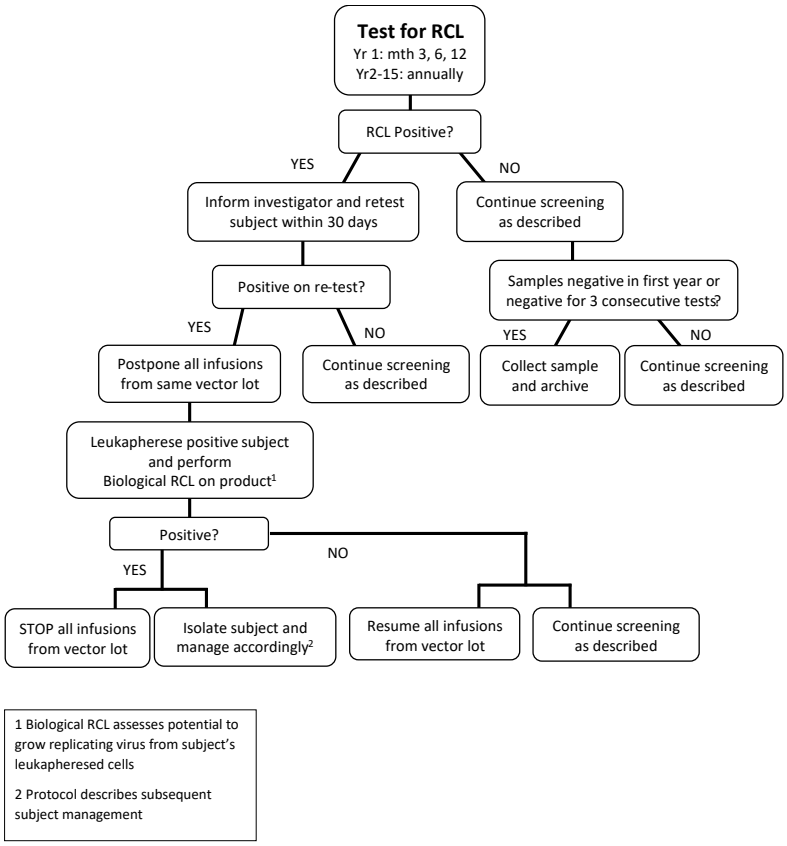
- If the second test is negative, then subject samples will continue to be tested for VSV-G DNA copies until VSV-G DNA copies are not detected for 3 consecutive annual assessments as described in Figure 1, at which time the subject samples will be collected and archived annually until year 15.
- If the second test is positive, infusions for all subjects receiving T-cells modified with the same vector lot will be postponed. The subject with the confirmed positive VSV-G signal will be scheduled for leukapheresis and a biological RCL test will be performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product [Manilla, 2005].
- If the biological RCL test is positive, all infusions using the same TCR in the interventional protocol(s) will be halted. An action plan will be discussed with FDA and other regulatory authorities and experts as appropriate. Additional subjects will not be treated with the same TCR until such time as a plan is completed, reviewed, and agreed upon.
- If the biological RCL test is negative, infusions for all subjects can resume.

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should a biological RCL be confirmed in a subject [FDA, 2020a]. However, because the probability and characteristics of a RCL are unknown, no concrete plans have been put in place. As of the writing of this protocol, it is agreed the subject must be isolated and no additional subjects will be treated with the same TCR until a plan is agreed upon as outlined above.

The following approaches have been discussed for subject management:

1. Intensive follow-up of subject in consultation with FDA, and other regulatory authorities, National Institutes of Health, gene therapy experts, Study Investigators, and HIV physicians.
2. Provide targeted antiretroviral therapies based on genotyping of the RCL.

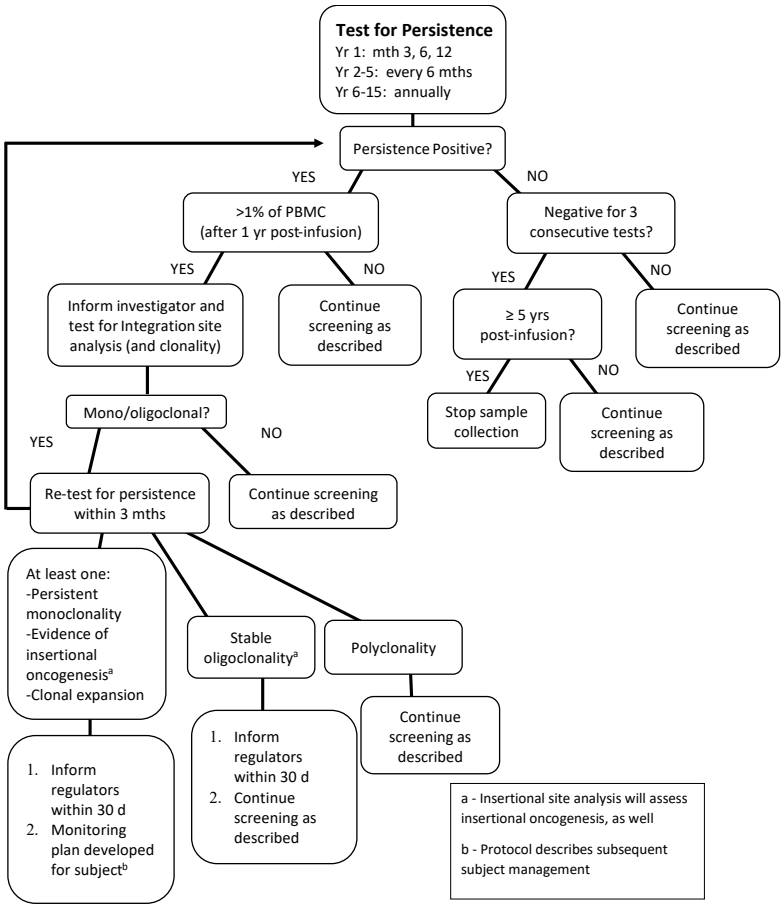
Figure 1: Flow Chart for Testing for Replication Competent Lentivirus (RCL)



PBMC samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects. Subject samples will be tested for persistence at 3, 6 and 12 months post-infusion and every 6 months for 5 years and annually from year 6-15 in accordance with the FDA and EMA guidance [FDA, 2020a; FDA, 2020b; EMA, 2009]. The scheme for testing for persistence is presented in Figure 2.

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

Figure 2: Flow Chart for Testing for Persistence



10.7.3. Integration Site Analysis

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

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

If there is clonal dominance in the genetically modified T-cell population (either monoclonality or oligoclonality) the persistence assessment will be repeated within 3 months on a new sample. If the repeated analyses demonstrate: 1) persistent monoclonality, 2) other evidence of IO (for example, integration of the vector in the promoter region of a known oncogene or tumor suppressor gene), or 3) clonal expansion (an increase in percent predominance of a clone), the DSMB and the Safety Governance Board will be notified. Adaptimmune will develop a monitoring plan specific to the health care risk and strategies to inform appropriate subjects, Investigators, FDA, and other regulators of the findings.

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

10.7.4. Letter to Physician - LTFU Notification

[date]

[name and address]

Dear [physician name],

Your subject [subject name] has participated in a clinical research study, A Phase 2 Open-Label Clinical Trial of ADP-A2M4CD8 in Subjects with Advanced Esophageal or Esophagogastric Junction Cancers, that requires 15-year monitoring for adverse events. To aid in reporting of adverse events that are possibly related to the clinical research study, we are asking the subjects on our research study to designate a primary care or infectious disease physician that may help in the monitoring and reporting of adverse events. Your subject has designated you. If upon any of your visits with your subject, any of the following events are reported or discovered, please contact the Study Nurse or Physician as soon as possible:

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

If your subject experiences any of these events, please refer them back to their Study Physician. Please contact the Study Coordinator below as soon as you can so that they can record the event and then monitor your subject's health if necessary. When you call, remember to mention the protocol number of the study which is ADP-005-002, subject ID [XXX] and the study title which is A Phase 2 Open-Label Clinical Trial of ADP-A2M4CD8 in Subjects with Advanced Esophageal or Esophagogastric Junction Cancers".

Study Physician:

Name: [Study Physician name]

Phone: [Study Physician phone]

Email: [Study Physician e-mail]

Study Coordinator:

Name: [Study Coordinator name]

Address: [Study Coordinator address]

Phone: [Study Coordinator phone]

Email: [Study Coordinator e-mail]

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

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

Best regards,

[Study Physician/Coordinator]

10.8. Appendix 8: Efficacy Reporting

10.8.1. RECIST 1.1 Criteria for Evaluating Response in Solid Tumors

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Ultrasound 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 PR and CR or evaluation of new or enlarging effusions to differentiate between PD and Response/SD).

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 (Table 12)

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

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

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).

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

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

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

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

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

Special notes on assessing progression of Non-Target lesions

PD: Unequivocal progression of existing non-target lesions.

- **When subject has measurable disease**. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target

disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

- **When subject has only non-measurable disease.** There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

New lesions

The appearance of new malignant lesions denotes disease progression:

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

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

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

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

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

Table 12: Summary of the best overall response status calculation at each time point

Target Lesions	Non-Target Lesions	New Lesions	Best Overall Response	Best Overall Response when Confirmation is Required[1]
CR	CR	No	CR	≥ 4 wks. Confirmation[2]
CR	Non-CR Non-PD	No	PR	≥ 4 wks. Confirmation[2]
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥ 4 weeks from ADP-A2M4CD8 infusion[2]
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD[3]	Yes or No	PD	
Any	Any	Yes	PD	

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

Confirmation

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

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

Missing Assessments and Inevaluable Designation

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

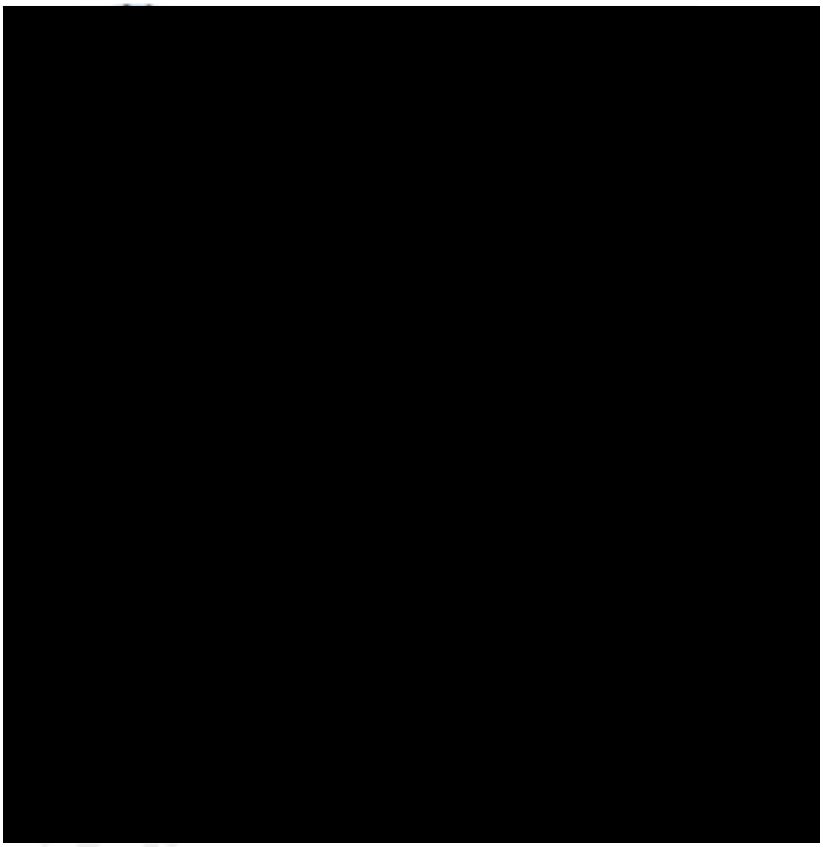
http://recist.eortc.org/recist-1-1-2/

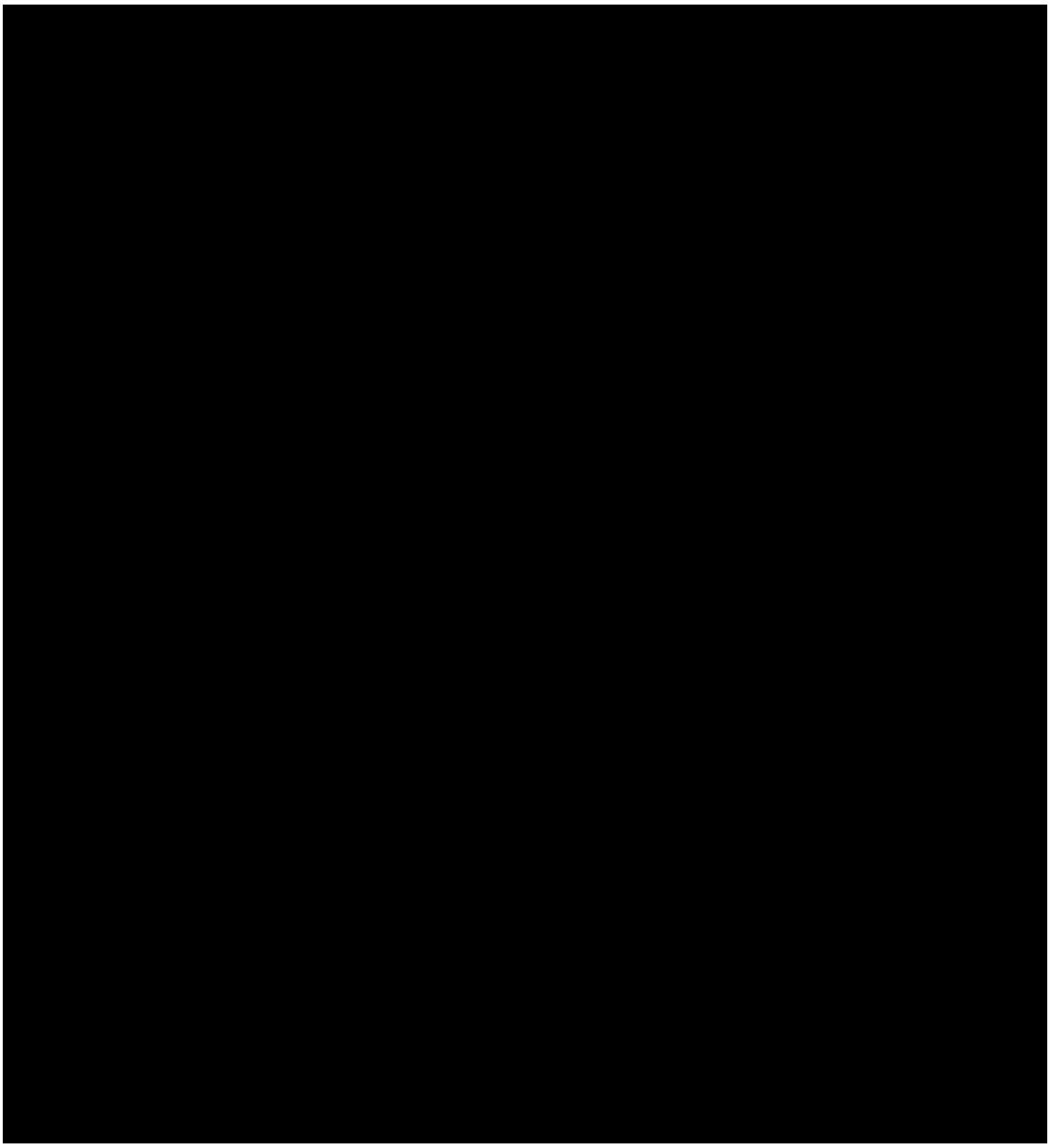
10.9. Appendix 9: ECOG Performance Status

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 housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[Oken, 1982]

10.10. Appendix 10: EQ-5D-3L Health Questionnaire (SAMPLE)





[redacted]

10.11. Appendix 12: Abbreviations

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

ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BOR	Best overall response
CAR	Chimeric antigen receptor
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computerized tomography
CTA	Cancer-testis antigen
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cell
DLCO	Diffusing capacity of the lung for carbon monoxide
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram

ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalography
EMA	European Medicines Agency
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose–positron emission tomography
FEV1	Forced expiratory volume
FSH	Follicle stimulating hormone
GEJ	Gastroesophageal junction
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-cell leukemia virus
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
ICF	Informed consent form
ICH	International Council for Harmonization
ICP	Intercranial pressure
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry

IND	Investigational new drug application
INR	International normalized ratio
IO	Insertional oncogenesis
IRAC	Independent radiological assessment committee
ISF	Investigator Site File
ISL	Investigator Safety Letter
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVD	*In vitro* diagnostic
IV	Intravenous
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
LMO2	LIM domain only 2
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MAGE-A	Melanoma-associated antigen-A
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
mITT	Modified Intent-to-Treat
MRCLS	Myxoid/Round Cell Liposarcoma
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MUGA	Multiple-gated acquisition
N/A	Not applicable
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OTC	Over the counter
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease

PDF	Portable document format
PET	Positron emission tomography
PFS	Progression-free survival
PP	Per-protocol
Psi	Packaging signal sequence
PR	Partial response
PTT	Partial thromboplastin time
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAEW	Serious adverse event worksheet
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SBT	Sequence based typing
SD	Stable disease
SIN	Self-inactivating
SPEAR	Specific peptide enhanced affinity receptor
SUSAR	Suspected unexpected serious adverse reactions
T&E	Time and Events
TCR	T-cell receptor
TLC	Total lung capacity
TTR	Time to response
ULN	Upper limit of normal
US	United States
USPI	United States product insert
VEGFR	Vascular endothelial growth factor receptor
VSV-G	Vesicular Stomatitis Virus G glycoprotein

10.12. Appendix 13: Protocol Amendment History

Protocol Version: Amendment 1.0 dated 29-June-2021 is replaced by Protocol Amendment Version 2.0 dated 17-November-2021.

Section amended in version 2.0	Change	Rationale for change
Throughout	Administrative updates to section numbering and addition of abbreviations.	Administrative updates for clarity.
Synopsis, T&E table, 5.2, 8.4.8	Addition of Inclusion Criteria #14 detailing oxygen support requirements.	Revised to reflect updated safety measures.
Synopsis, T&E table, 5.3, 8.4.9.4	Update to Exclusion Criteria #8 to Pulmonary Function Test requirements and requirements for oxygen support.	Revised to reflect updated safety measures.
4.1	Update to statistical methodology.	Correct error in previous protocol versions.
Table 4	Correction to lymphodepletion dosing and addition of footnote to allow use of institutional guidelines.	Revised to correct error and to allow use of institutional guidelines.
10.5.6	Update to the Management of Cytokine Release Syndrome.	Revised to reflect updated safety measures and to align with 2020 SITC guidelines.

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