Study Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

NCT number: NCT04044768

Document: Protocol

Document Date: 05 Feb 2021

PROTOCOL NUMBER ADP-0044-002

A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

(SPEARHEAD 1 STUDY)

PROTOCOL VERSION: AMENDMENT 3

DATE: 05FEB2021

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T Cells in Subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma (MRCLS)

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-A2M4 Investigator's Brochure.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T Cells in Subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma (MRCLS)

Product Name: ADP-A2M4

Protocol Number: ADP-0044-002

IND Number: 17235

EudraCT Number: 2019-000589-39

DATE OF ORIGINAL PROTOCOL: 25FEB2019

Amendment Number	Date	Reason for Change
Original	25FEB2019	NA –
Amendment 1	04JUN2019	Change in the lymphodepletion regimen Addition of ECG at Day 5 Added upper age limit Increase entry criteria for ANC, platelets, GFR Additional exclusion criteria under uncontrolled intercurrent illness Emerging data for ADP-A2M4 added Updated study physician Administrative changes

Amendment Number	Date	Reason for Change
Amendment 2	26MAR2020	Update to sponsor contacts Updates and clarifications to HLA criteria Removed futility analysis and associated protocol aspects Updated number of subjects Decreased duration of enrollment Increased LVEF criteria Clarification of washout for prior gene therapy Added updated data from current ADP-A2M4 Investigator's Brochure Update to CRS management guidelines Updated Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells Administrative changes and clarifications

Amendment Number	Date	Reason for Change
Amendment 3	05FEB2021	Update to sponsor contacts Addition of Cohort 2 (45 synovial sarcoma subjects) Updates to safety and efficacy information to align with current IB Information added for COVID-19 requirements Exclusion for compression/occlusion of a vital structure added Addition of EORTC QLQ-C30 (Cohort 2 only) Removal of CDx and PP Population definitions Additional details added throughout for addititional clarity of wording Template language updated

CONFIDENTIALITY STATEMENT

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

[redacted]

15-Feb-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]
Secondary Sponsor Study Physician	[redacted]	[redacted]	[redacted]	[redacted]

Sponsor Details:

Adaptimmune LLC
351 Rouse Blvd
Philadelphia, PA 19112
USA

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma	
Short Title	SPEARHEAD 1 Study
Protocol Number	ADP-0044-002
Phase	2
Methodology	Subjects with advanced synovial sarcoma or myxoid/myxoid round cell liposarcoma (Cohort 1 only) will be Pre-screened to determine appropriate human leukocyte antigen (HLA) and tumor antigen status. Only subjects with advanced synovial sarcoma will be eligible for Cohort 2. Only subjects expressing at least 1 HLA-A*02 inclusion allele and no exclusion allele and whose tumor expresses the MAGE-A4 antigen above the 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 into either Cohort 1 or Cohort 2. Enrolled subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the ADP-A2M4 cell Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation. Subjects who have enrolled into a Cohort may not enroll into the other Cohort subsequently. Prior to the administration of lymphodepleting chemotherapy all eligibility criteria will be reconfirmed and baseline tumor assessment obtained. Anticancer therapy may be administered between screening and leukapheresis and between leukapheresis and the start of lymphodepletion (bridging therapy), if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods must be adhered to. When the ADP-A2M4 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5) followed by infusion of ADP-A2M4 cells on Day 1. Subjects will remain hospitalized for observation for at least 24 hours post T cell infusion.

	An independent Data Safety Monitoring Board (DSMB) will review the ongoing safety during the interventional phase of the study for Cohort 1. Cohort 2 will begin once all subjects have been dosed in Cohort 1. Subjects in both cohorts will have the following study visits for assessment of eligibility, efficacy, safety, health related-outcome and biomarkers: Pre-Screening, Screening, Leukapheresis, Baseline, Lymphodepleting Chemotherapy (Day -7 to Day -4), T cell infusion (Day 1) and immediate post infusion monitoring (Day 1 through Day 8), weekly visits until Week 4 post infusion, then 6, 8, 12, 16 and 24 weeks then every 2 months until disease progression. Subjects will undergo disease monitoring by magnetic resonance imaging (MRI) or computerized tomography (CT) scan at Screening, Baseline, Week 4, Week 8, Week 12, Week 16 and Week 24, and every 2 months 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 6-15. The timepoint at which the subject switches will be driven by the timepoint at which the subject progresses e.g. 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 Primary Efficacy Analysis will be for Cohort 1 only. Clinical cut-off for the primary analysis will occur once the forty-fifth subject dosed in Cohort 1 has up to 6 months follow-up post T cell infusion. At this time, all safety and secondary efficacy endpoints for Cohort 1 only will also be summarized to provide supportive evidence to the primary assessment.
Study Duration	Enrollment is expected to continue for approximately 12 months for Cohort 1 and for an additional 12 months for Cohort 2. The study will be considered complete once all enrolled subjects complete 15 years of follow-up or discontinue the study for any reason.
Study Center(s)	The study will be conducted in approximately 24 sites in North America and Europe. Additional sites may be added at the discretion of the Sponsor.
Number of subjects	Ninety (90) subjects: Forty-five (45) synovial sarcoma and MRCLS subjects in Cohort 1; Forty-five (45) synovial sarcoma subjects in Cohort 2.

Objectives	Endpoints
Primary	
To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	Overall Response Rate (ORR) per RECIST v1.1 by independent review in Cohort 1.
Secondary	
To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	For Cohort 1 and across Cohorts (overall): • 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-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review across Cohorts (overall) For Cohort 1 and across Cohorts (overall): • Time to Response (TTR) • Duration of Response (DoR) • Best Overall Response (BOR) • Progression Free Survival (PFS) • Overall Survival (OS)
Development and validation of an in vitro diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Across Cohorts: • Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay
Characterize the in vivo cellular pharmacokinetics (PK) profile of ADP-A2M4 cells	For Cohort 1 and across Cohorts (overall): • Peak persistence and other relevant PK parameters of ADP-A2M4 cells
Exploratory	

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Inclusion Criteria	1. Subject (or legally authorized representative) voluntarily agrees to participate by giving written Informed Consent (and Assent as applicable) in accordance with ICH GCP guidelines and applicable local regulations. 2. Subject (or legally authorized representative) agrees to abide by all protocol required procedures including study related assessments and management by the treating institution for the duration of the study, including long term follow-up. 3. Age ≥16 and <75 years at the time the Pre-screening informed consent/assent is signed. 4. Diagnosis of advanced (metastatic or inoperable) synovial sarcoma or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by cytogenetics. Inoperable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise. a. For Synovial Sarcoma (Cohort 1 and Cohort 2): confirmation by the presence of a translocation between SYT on the X chromosome and

	SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)). b. For MRCLS (Cohort 1 only): confirmation by the presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) or t(12; 22) (q13;q12). 5. Must have previously received either an anthracycline or ifosfamide containing regimen. 1st-line metastatic treatment with ADP-A2M4 is permissible if ifosamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumour setting.(Subjects who are intolerant of both anthracycline and ifosfamide must have previously received at least one other type of systemic therapy). 6. Measurable disease according to RECIST v1.1. 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. 8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥2+ staining in ≥30% of the cells by immunohistochemistry. 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%. 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 an 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 a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide).

	13. Must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support) within 7 days prior to lymphodepletion and leukapheresis
Platelets	≥ 100 x10^9/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Coagulation	
Prothrombin Time (PT) or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation
Renal	
Glomerular filtration rate (calculated CrCl using only the Cockcroft-Gault equation, or measured using either a 24-hr urine creatnine collection or a radionuclide EDTA test)[a]	≥ 60 mL/min

<table>
<tr><td></td><td colspan="2">Hepatic</td></tr>
<tr><td></td><td>Serum total bilirubin</td><td>≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin

<35% of total bilirubin)</td></tr>
<tr><td></td><td>Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT)</td><td>≤ 2.5x ULN</td></tr>
<tr><td></td><td colspan="2">a) 24-hour urine creatine clearance or radionuclide EDTA tests should be used to measure the GFR in all subjects: ≥ 65 years old; clinically obese (≥ 30KG/m^2) or underweight (≤18.5KG/m^2); borderline low calculated CrCl (Cockcroft-Gault) at approximately 60mls/min.

Renal function will be reassessed at Baseline using the same methodology.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="2">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:
<table>
<tr><th>Treatment/Therapy</th><th>Required Wash-out Prior to Leukapheresis</th><th>Required Wash-out Prior to Lymphodepletion</th></tr>
<tr><td>Cytotoxic chemotherapy</td><td>3 weeks</td><td>3 weeks</td></tr>
<tr><td>Tyrosine kinase inhibitor (TKI) (e.g. pazopanib)</td><td>1 week</td><td>1 week</td></tr>
<tr><td>Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors,)</td><td>4 weeks</td><td>4 weeks</td></tr>
<tr><td>Anti-cancer Vaccine</td><td>8 weeks in the absence of tumor response. The subject</td><td>8 weeks in the absence of tumor response.</td></tr>
</table>
</td></tr>
</table>

			should be excluded if their disease is responding to an experimental vaccine given within 6 months	The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months
		Gene therapy using an integrating vector	Subjects who have received a gene therapy using any DNA-integrating vector other than a lentivirus (retrovirus, AAV, etc.) are excluded from this study. Subjects who have received a gene therapy using a lentiviral vector may be eligible if they have persistence results below the lower limit of quantification (LLOQ) for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.	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 6.5.1 for exceptions.	2 weeks	2 weeks

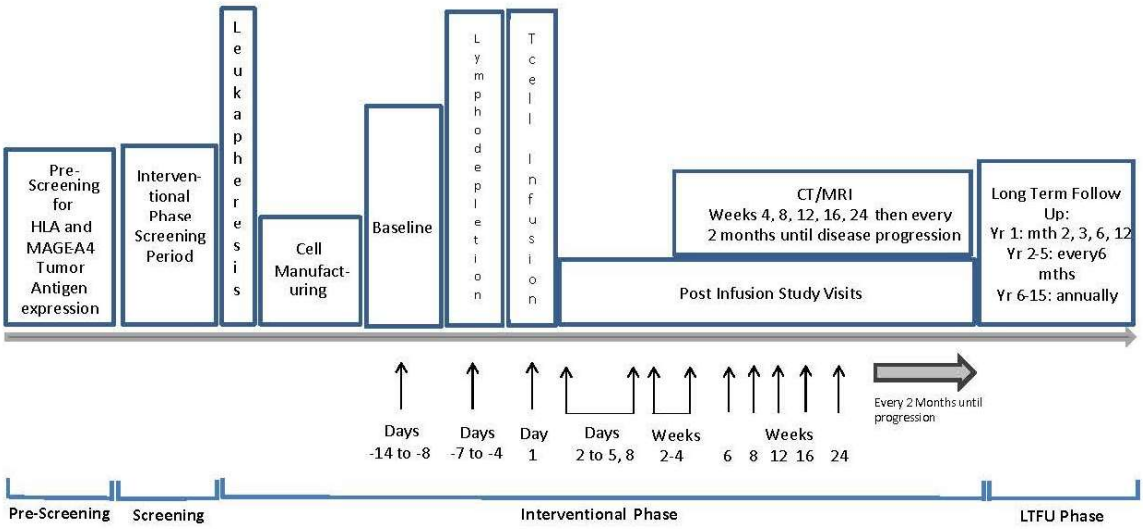
		Investigational treatment or interventional clinical trial	4 weeks	4 weeks
		Allogeneic hematopoietic stem cell transplant	Not permitted within any amount of time	Not permitted within any amount of time
		Radiotherapy to the target lesions	N/A	3 months. A lesion with unequivocal progression may be considered a target lesion regardless of time from last radiotherapy dose. (Note: there is no washout period for palliative radiation to non-target organs).
		Major surgery	N/A	4 weeks. Subjects must have recovered from any surgical 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, 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. Symptomatic CNS metastases including leptomeningeal disease. Subjects with a prior history of symptomatic CNS metastasis including leptomeningeal disease must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiation (WBRT) and/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. 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; • Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4; • Uncontrolled clinically significant arrhythmia; • Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months; • Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent); • Congenital or family history of long QT syndrome; • Current uncontrolled hypertension despite optimal medical therapy; • History of stroke or central nervous system bleeding; transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) in last 6 months; • Incipient compression/occlusion of a vital structure (e.g. bronchus; superior vena cava; renal outflow tract) which cannot undergo prophylactic stenting; • COVID-19 infection or a positive COVID-19 RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy. If a subject has a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart.

	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 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.
Investigational Product, Dose, Route, Regimen	ADP-A2M4 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 primary clinical endpoint for efficacy is Overall Response Rate (ORR) defined as the proportion of subjects with a complete response (CR) or partial response (PR) via independently reviewed RECIST v1.1 relative to the total number of subjects in the analysis population in Cohort 1. The primary analysis population for safety and efficacy will be the modified intent to treat population (mITT) defined as all subjects who received the ADP-A2M4 cell infusion in Cohort 1. (Null Hypothesis) H_0: $p \leq p_0$, vs. (Alternate Hypothesis) H_1: $p > p_0$, where p_0 (historical control rate) = 0.18. Statistical assumptions include: • The type I error (α) will be no more than 0.025 • The type II error (β) will not exceed 0.1 • Exact Binomial methods will be used to test the hypothesis

	• The assumed ORR for ADP-A2M4 is 0.40 Based on the statistical design assumptions above and the hypotheses and clinical assumptions detailed in Section 9, the estimated sample size for the trial is 45 subjects in Cohort 1 for the primary analysis. An additional 45 subjects are to be enrolled in Cohort 2, although no formal hypothesis testing is planned for Cohort 2 or overall (across cohorts). The primary endpoint, ORR per RECIST v1.1 by independent review for Cohort 1, will be evaluated using a one-sided exact-based Clopper-Pearson 97.5% confidence interval (CI). If the lower bound of the 97.5% CI exceeds 18%, the trial has met the pre-specified threshold for demonstrating efficacy. The key secondary efficacy endpoints ORR per RECIST v1.1 by independent review across Cohorts (overall), TTR, DoR, 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. Two-sided 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, PK profile, 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. Efficacy and safety summaries will be displayed across tumor types (overall) and by tumor type. Efficacy and safety summaries will be displayed across cohorts (overall) and by cohort as indicated above. Other subgroups may be explored and these will be described in the Statistical Analysis Plan.

1.2. Schema


Pre-Screening for HLA and MAGE-A4 Tumor Antigen expression
Interven-tional Phase Screening Period
Leukapheresis
Cell Manufact-uring
Baseline
Lymphodepletion
T cell Infusion
CT/MRI
Weeks 4, 8, 12, 16, 24 then every 2 months until disease progression
Post Infusion Study Visits
Long Term Follow Up:
Yr 1: mth 2, 3, 6, 12
Yr 2-5: every6 mths
Yr 6-15: annually
Days -14 to -8
Days -7 to -4
Day 1
Days 2 to 5, 8
Weeks 2-4
Weeks 6 8 12 16 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

Table 1: T&E for Pre-Screening and Interventional Phase

Written Informed Consent must be obtained prior to performing any protocol procedures. A Pre-screening 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.

			Interventional Phase																							
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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																									Section 8.1.1
Inclusion/Exclusion	X	X		X																						Section 5
Disease History	X	X																								Section 8.1.2
HLA typing	X[12]																									Section 8.2.1

			Interventional Phase																							
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
MAGE-A4 Expression	X																								Section 8.2.2
Cytogenetics testing for translocations		X[1]																							Section 8.2.3
Safety and Efficacy Assessments																									
Medical History		X																							Section 8.4.1
Physical Exam		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	Section 8.4.4
ECOG		X		X										X	X	X	X	X	X	X	X	X	X	X	Section 8.4.5

			Interventional Phase																					
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Height				X																					
Weight		X		X													X		X	X	X	X		X	Section 8.4.7
Vital Signs		X		X					X[2]	X	X	X	X	X	X									X	Section 8.4.6
ECG		X		X					X[3]				X												Section 8.4.8.1
Echo/MUGA		X																							Section 8.4.8.2
CT / MRI		X		X													X[14]		X[14]	X[14]	X[14]	X	X	X	Section 8.3.1
Brain MRI				X[4]																					Section 8.4.9
ICE									X	X	X	X	X	X											Section 8.4.19
GFR (estimated or measured)		X		X																					Section 8.4.10

			Interventional Phase																						
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Hematology		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.11
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 8.4.12
Coagulation		X		X																					Section 8.4.13
Pregnancy Test		X		X																					Section 8.4.16
Infectious Disease Screening		X																							Section 8.4.17
CMV PCR				X[5]					X[5]						X[5]		X[5]	X[5]	X[5]						Section 8.4.18
Thyroid Function Tests				X																					Section 8.4.14
C-reactive Protein[6]				X					X			X		X	X		X								Section 8.4.20
Ferritin[6]				X					X			X		X	X		X								Section 8.4.21

	Interventional Phase																							
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**												**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
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
Persistence (Vector Copies)	X[10]	X[10]		X						X		X		X	X		X		X	X		X	X		Section 8.4.22 LTFU Table 2
RCL (VSV-G DNA)				X																X		X	LTFU Table 2		Section 8.4.23 LTFU Table 2
Leukapheresis, Lymphodepleting Chemotherapy and Investigational Product Administration																									
Leukapheresis			X																						Section 6.1
Fludarabine[11]					X[11]	X[11]	X[11]	X[11]																	Section 6.2
Cyclophosphamide					X	X	X																		Section 6.2
ADP-A2M4 Infusion									X																Section 6.3
Biomarker Assessments																									

			Interventional Phase																						
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Tumor Biopsy				X													X[5]							X	Section 8.6.1
Cytokine and Soluble Protein Analyses[6]				X					X[6]	X		X		X	X		X		X	X		X	X		Section 8.6.2
Liquid Biopsy (Blood Plasma)				X					X[3]								X[7]		-					X	Section 8.6.3
Cell Phenotyping and Functional Assays				X					X					X	X		X		X	X		X	X	X	Section 8.6.4
Patient Reported Outcomes																									

			Interventional Phase																						
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
EQ-5D-3L				X															X		X	X	See footnote 9		Section 8.7.1
EORTC-QLQ-C30 (Cohort 2 only)				X															X		X	X	See footnote 13		Section 8.7.2

[1] Screening Visit 2 assessments should be completed within 28 days of leukapheresis; CT/ MRI scans and ECHO/MUGA scans, performed as standard of care within 4 weeks prior to Screening Visit 2 (prior to study consent) are acceptable. Cytogentic confirmation of diagnosis can be historic, done as standard of care or be done any time after signing Treatment Consent and does not need to be within 28 day screening window.
[2] Measured pre-infusion, and at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started
[3] Pre-infusion
[4] Within 4 weeks of lymphodepletion
[5] If CMV seropositive at screening, CMV-PCR done at baseline. All CMV seropositive subjects will continue to be monitored by CMV PCR at day 1, week, 2, 4, 6, 8
[6] 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
[7] Can be taken anytime between Week 3 and Week 8
[8] Day 1 samples taken pre-infusion and 2-4 hr. post-start of infusion

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

[10] Only for a subject who has previously received a gene therapy using a lentiviral vector. Subject's must have results below the LLOQ for at least 2 samples taken at least 1 months apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.

[11] Fludarabine dose must be adjusted for renal impairment using the Cockcroft-Gault equation/methods described in Section 6.2.1

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

[13] EORTC-QLQ-C30 is for Cohort 2 subjects only; EORTC-QLQ-C30 will also be done at Month 12 if the subject remains in the interventional phase of the study

[14] On study scans from Week 4 through Week 16 should be at least 28 days apart to ensure compliance with RECIST 1.1 requirement for confirmatory scans in the event that an objective response is noted by central read

1.3.2. Long Term Follow Up Phase Time & Events Table

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

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 Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.2
Mutagenic agents, other investigational agents or anti-cancer therapies	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 8.4.11
Clinical chemistry	X	X	X	X		X		X		X		X	X	Section 8.4.12
Vector Copies (Persistence)	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.22
VSV-G DNA (RCL)		X	X	X		X		X		X		X	X	Sections 8.4.23

2. INTRODUCTION

2.1. Study Rationale

2.1.1. Rationale for using MAGE-A4 TCR in synovial sarcoma and myxoid/round cell liposarcoma

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

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

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

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-A2M4 are autologous CD4 and CD8 positive T cells that have been transduced with a self-inactivating lentiviral vector expressing a high affinity MAGE-A4 specific T cell receptor (TCR). MAGE-A4 is a cancer/testis antigen (CTA) that has restricted expression in normal tissue, and is expressed across a range of solid tumors at varying frequencies.

ADP-A2M4 recognizes the MAGE-A4230-239; GVYDGREHTV peptide derived from the MAGE-A4 family of CTAs. Thus, ADP-A2M4 incorporates an affinity enhanced TCR capable of recognizing the human leukocyte antigen (HLA)-A*02-GVYDGREHTV antigen complex.

The safety of ADP-A2M4 has been shown in subjects with different tumor types in an ongoing Phase 1 study (NCT03132922). Data of another genetically engineered T cell investigational product, NY-ESO^{c259}T, in synovial sarcoma provides evidence that TCR therapies can be effective in solid tumors [D'Angelo, 2018a].

2.2. Background

2.2.1. MAGE-A4 background

The cancer/testis antigens (CTA) comprise a number of genes that have restricted expression to the testis, but have been identified by their expression in various tumor types [Caballero, 2009]. These include NY-ESO-1, MAGE-A family, SSX2, BAGE, GAGE, and CT7 among others.

Most of these testis-specific genes are coded on the X chromosome. Several of these antigens, including MAGE-A3, MAGE-A10 and MAGE-A8, also have expression in placenta [Caballero, 2009]. In general, melanoma, ovarian cancer and lung cancer, particularly of the squamous cell type, have the highest frequency of RNA expression across the CTAs. Epithelial cancers such as breast, bladder and prostate cancer have intermediate expression, with frequency of mRNA expression in the range of 30% to 50%. CTAs often have coordinated expression, with several expressed in a single tumor [Gure, 2005]. In addition to RNA, immunohistochemistry is often used to determine the expression levels of CTAs. While it is generally seen that mRNA expression of these antigens correlates well with protein expression it should be noted that there is frequently heterogeneous expression of protein across the tumor, with strong expression in a small subset of tumor cells. There is also epigenetic and post-transcriptional modification that determines protein expression levels under certain conditions.

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

MAGE-A4 has been described as having high expression in synovial sarcoma and MRCLS. A recent study showed that 82% of synovial sarcoma samples expressed MAGE-A4 when evaluated by Immunohistochemistry (IHC) and high expression of NY-ESO-1 and MAGE-A4 was significantly correlated with the presence of necrosis and advanced clinical stage [Iura, 2017a]. [redacted]. A further report suggested that 67.7% of MRCLS samples, express MAGE-A4 [Iura, 2017b]. [redacted]

2.2.2. Discovery of ADP-A2M4

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

The Investigational Product (IP) is comprised of autologous CD4 and CD8 T cells obtained from eligible subjects who have MAGE-A4 expressing tumors and who are HLA-A*02 positive. Subjects who are HLA-A*02:05 are excluded because alloreactivity has been observed in vitro with ADP-A2M4 to this HLA allele. The T cells undergo self-inactivating (SIN) lentiviral transduction with ADP-A2M4 specific nucleic acid under Good Manufacturing Practice (GMP) conditions. The resulting polyclonal ADP-A2M4 specific peptide enhanced affinity receptor (SPEAR™) T cells are now genetically engineered to target the antigen on the subject's MAGE-A4 positive advanced tumor.

2.2.3. Synovial sarcoma/MRCLS current therapies and Emerging Data from ADP-A2M4 and other TCRs

Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

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

Synovial Sarcoma

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

Surgery is the standard therapy for localized disease. Patients with advanced synovial sarcoma receive ifosfamide and/or doxorubicin, as the first-line of therapy [ESMO, 2014]. Doxorubicin-based first-line metastatic doublet therapies, such as doxorubicin in combination with the anti-

PDGFR alpha monoclonal antibody olaratumab [Lilly, 2019], have not demonstrated improved clinical benefit compared to single-agent doxorubicin.

There is no specific standard of care (SoC) in second line therapies and beyond. Pazopanib is approved in the U.S and in Europe for patients with synovial sarcoma previously treated with chemotherapy [Votrient™ US Prescribing Information, EU SmPC]. A randomized double blind placebo controlled Phase 3 trial of pazopanib was conducted in patients with advanced STS. Overall response rate (ORR) as assessed by Data Safety Monitoring Board (DSMB) for the intent to treat (ITT) population was 4%, median duration of response (DoR) of 9 months, and median progression free survival (PFS) of 4.6 months compared with 1.6 months for placebo (HR=0.35, p<0.001). Median overall survival (OS) was 12.6 months compared with 10.7 months for placebo (HR=0.87; 95% CI: 0.67, 1.12). Only 38 subjects with synovial sarcoma (randomized 2:1) were included in the study with a median PFS of 4.1 months in the pazopanib arm vs 0.9 months for placebo (HR= 0.43; 95% CI 0.19, 0.98). The response rate is not reported by histology [Votrient™ US Prescribing Information, EU SmPC]. In a Phase 2 non-randomized study of pazopanib (EORTC Study 62043), responses as assessed by the Investigator were reported in 5/37 (13%) subjects with synovial sarcoma [Sleijfer, 2009].

The response rate in a retrospective analysis of gemcitabine and docetaxel in patients with synovial sarcoma was 10% [Abouharb, 2014]. Several other agents have shown no appreciable anti-tumor activity in synovial sarcoma; these include many novel classes of agents such as HDAC-inhibitors [Cassier, 2013], IGF-1R antibodies [Pappo, 2014; Olmos, 2010], mTOR inhibitors [Schwartz, 2013], vascular disrupting agents [Blay, 2015] and anti-CTLA4 antibodies [Maki, 2013].

Effective treatment options for patients with advanced relapsed synovial sarcoma are limited. The median survival upon relapse from first-line therapy is approximately 12 months [Minchom, 2010] and the ORR from prospective trials for existing therapies ≤ 13%.

Thirty-eight subjects have received treatment with a single dose of ADP-A2M4 up to 9.9756 x 10^9 transduced cells within the phase 1 ADP-0044-001 study. Synovial sarcoma subjects represent the most frequent tumor type in the study and the majority of the subjects treated in Group 3/Expansion. Of the 16 subjects with synovial sarcoma, most subjects were males (62.5%), most subjects were White (87.5%) and the median age was was 49.0 years (range 31 to 76 years). The median ADP-A2M4 dose in synovial sarcoma was 9.28 x 10^9 transduced cells (range: 3.4 to 10 x 10^9). The reported adverse events are consistent with those typically experienced by patients with advanced cancer undergoing cytotoxic chemotherapy or cancer immunotherapy (e.g, cytopenias, fatigue, CRS). The most common AE ≥ Grade 3 occurring in ≥ 25% of subjects with synovial sarcoma were, lymphopenia/lymphocyte count decreased (100%), leukopenia/WBC count decreased (93.3%), neutropenia/neutrophil count decreased (88%), neutropenia/neutrophil count decreased (81%), anemia/RBC decreased (44%), thrombocytopenia/platelet count decreased (44%), hypophosphatemia (44%), rash (19%), CRS (13%), decreased appetite (6%) and hypotension (6%). Cytokine release syndrome (any Grade) was reported in 88% of the subjects with synovial sarcoma. There was one (1) Grade 5 SAE of prolonged pancytopenia with hypoplastic bone marrow considered possibly related to ADP-A2M4. In subjects with synovial sarcoma, the ORR (confirmed responses) was 44% (95%CI:

16.34, 67.71). The Best Overall Response was PR (7), SD (8), and PD (1).Disease control rate was 94% with 11 patients still alive at time of 1-September-2020 data cut-off. Subject responses were durable with a median duration of response of 28 weeks (range: 12-72 weeks). [CTOS 2020]. This data supports the continued evaluation of ADP-A2M4 in advanced/metastatic synovial sarcoma.

Myxoid/Round Cell Liposarcoma (MRCLS)

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

Treatment involves the wide surgical excision of the tumor and surrounding tissue. Myxoid round cell liposarcoma may be treated with pre-operative chemotherapy and/or pre-operative or post-operative radiotherapy [NCCN, 2012]. Doxorubicin and ifosfamide are the first line systemic treatment options for patients with metastatic disease. Retrospective analyses in previously untreated patients demonstrated response rates of ~38 - 45% [Jones, 2005; Katz, 2012]. Once patients relapse or develop metastatic disease treatment is aimed at slowing that pace of progression. A variety of therapies are used in the second-line setting and beyond although only trabectedin and eribulin are approved. A randomized open label phase 2 study of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma enrolled 270 patients. Patients were randomized to receive either a 24 hour infusion of 1.5 mg/m^2 of trabectedin once every 3 weeks, or a 3 hour infusion of 0.58 mg/m^2 of trabectedin once every week for three weeks of a 4 week cycle. The treatment regimen that was determined to be most beneficial was the 24 hour infusion of 1.5mg/m^2 of trabectedin once every 3 weeks. One hundred and thirty six patients were randomized to this arm of the study and the ORR was 5.6% [Demetri, 2016].

A subsequent randomized, phase 3, open-label, active-controlled trial comparing trabectedin (n=345) treatment with dacarbazine (n=173) in patients with unresectable, locally advanced or metastatic leiomyosarcoma (73%) or liposarcoma (27%) (dedifferentiated, myxoid round cell, or pleomorphic) and previous treatment with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen demonstrated an overall response rate (ORR of 9.9% (CI 0.72, 3.2) with trabectedin, an improvement of median progression-free survival (PFS) of 5.6 vs 1.5 months on dacarbazine but no difference in overall survival [Demetri, 2016]. Eribulin demonstrated an improvement in survival (median OS 13.5 vs 11.5 months; HR= 0.768; 95% CI, 0.618; 0.954) compared with darcarbazine in subjects with liposarcoma and leiomyosarcoma who received 2 or more prior lines of therapy. There was no difference in PFS and ORR was 3.9% with Eribulin and 4.9% with darcarbazine in all patients enrolled. In patients with liposarcoma the response rate was 1.4% [Schöffski, 2016]. Despite the approval of these two agents, overall survival in patients with relapsed disease remains 12-13 months [Demetri, 2016; Schöffski, 2016] and the ORR from prospective trials for existing therapies is < 10%.

A TCR T-cell product targeted against the NY-ESO-1 cancer testsis antigen has shown potentially promising clinical activity in eight MRCLS subjects [D'Angelo, 2018b]. For MAGE-A4, in Study ADP-0044-001, two MRCLS subjects were dosed with ADP-A2M4 cells. At the time of Data cut-off, 1 Sept 2020, no MRCLS subjects had responded to ADP-A2M4. ADP-A2M4 was however safe and well tolerated in MRCLS subjects in this phase 1 trial.

2.2.4. Benefit : Risk Assessment

The results of clinical and non-Clinical studies conducted with ADP-A2M4 cells are summarized in the ADP-A2M4 Investigator's Brochure. This section outlines the potential benefits, risks and the overall benefit: risk for this study.

2.2.4.1. Benefit

Although the basis for including both synovial sarcoma and MRCLS subjects in Cohort 1 of this study was the reported high frequency of MAGE-A4 expression in both synovial sarcoma and myxoid liposarcoma [Iura, 2017a; Iura, 2017b], as well as the historical clinical activity of the NY-ESO-1 TCR in both synovial sarcoma and MRCLS, preliminary evaluation of MRCLS response and MAGE-A4 antigen status in both the ADP-0044-001 and Cohort 1 ADP-0044-002 studies would suggest that ADP-A2M4 is not as clinically active in MRCLS as it is in synovial sarcoma possibly because of a comparatively lower MAGE-A4 antigen score distribution.

For these reasons, Cohort 2 will only enroll subjects with synovial sarcoma as such patients are likely to derive the greatest therapeutic benefit from the ADP-A2M4 cell product especially since study ADP-0044-001 has shown an ORR of 44% in sixteen heavily pre-treated metastatic synovial sarcoma subjects who had a median of three prior lines of treatment [CTOS 2020]. This data from study ADP-0044-001 in combination with emerging efficacy findings for synovial sarcoma subjects in Cohort 1 of study ADP-0044-002 would indicate that ADP-A2M4 is a promising cell product in metastatic synovial sarcoma especially since there is no specific standard of care beyond first-line ifosfamide and/or doxorubicin for patients with advanced (inoperable)/metastatic synovial sarcoma.

2.2.4.2. Risk

The safety and tolerability of ADP-A2M4 is being assessed in phase 1 trial (study ADP-0044-001) across multiple tumor types and in the ongoing Cohort 1 of study ADP-0044-002 including synovial sarcoma and MRCLS. Toxicities observed with ADP-A2M4 are common to other TCR or CAR-T therapies or standard of care chemotherapies.

Toxicities such as CRS, ICANS and pancytopenia/aplastic anemia are specific to TCR and CAR-T therapies and therefore guidelines for management of these events are included in Section 10.5. An advantage of TCR therapy is that they are generally administered once, and the vast majority of toxicities resolve within 4 to 6 weeks after T cell infusion.

Alloreactivity, whereby TCRs reactive towards a given peptide-MHC complex display cross-reactivity towards different HLA allelic variants, is a theoretical risk. Pre-clinical data indicate strong anti-HLA-A*02:05 alloreactivity, making A*02:05 an exclusion allele. Data also indicate

decreased potency against MAGE-A4230-239 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-A2M4 and 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: 1) extensive preclinical evaluation of the ADP-A2M4 which has incorporated learnings from other adoptive T cell therapy programs [ADP-A2M4 Investigator 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 cytokine release syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and pancytopenia/aplastic anemia as well as preventive measures for infectious complications, and 6) a Data Safety Monitoring Board (DSMB) to evaluate safety during the course of Cohort 1.

The potential risks for Cohort 2 (synovial sarcoma only) are expected to be similar to the emerging safety profile in Cohort 1 of study ADP-0044-002, as well as similar to the safety profile reported in the sixteen synovial sarcoma subjects previously dosed in the phase 1 trial, study ADP-0044-001 [CTOS 2020]. Moreover, when combined with the emerging safety profile in Cohort 1, the additional 45 synovial sarcoma subjects in Cohort 2 will permit a more deeper understanding and a better estimate of the frequency of adverse events of special interest (AESI) i.e. incidence of CRS, ICANS and pancytopenia in synovial sarcoma subjects treated with ADP-A2M4 cells compared to safety data from Cohort 1 alone.

2.2.5. Overall benefit: risk conclusion

In Cohort 1, based on the initially promising emerging efficacy and safety findings from the Phase 1 ADP-A2M4 SPEAR™ T-cell trial (study ADP-0044-001), it was jusfifable from a benefit-risk perspective to treat subjects with both advanced synovial sarcoma and MRCLS as they each constituted patient populations with a high unmet medical need, albeit with distinctly different metastatic disease natural histories. However, as more mature data has accrued from study ADP-0044-001 in combination with emerging findings from Cohort 1 of this ongoing Phase 2 trial (see Section 4.2., below), it has become apparent that ADP-A2M4 cells may potentially be less clinically active in MRCLS compared to synovial sarcoma. Therefore, at this time, continued evaluation of ADP-A2M4 treatment in Cohort 2 is only justifiable for synovial sarcoma subjects from a therapeutic benefit perspective. In regard to mitigation of risks, measures to ensure safe administration of ADP-A2M4 have been included in this study protocol, with close monitoring for toxicities and guidelines for their management.

The potential risks identified in association with ADP-A2M4 are justified by the anticipated benefits which may be afforded to patients with advanced (inoperable)/metastatic synovial sarcoma in Cohort 2. Indeed, real-world evidence in metastatic synovial sarcoma suggests that

pazopanib - which is approved for 2nd-line metastatic soft tissue sarcoma treatment in the United States and Europe - is not the most frequently administered 2nd-line therapy at several major synovial sarcoma centres in the United States possibly because of its low ORR [Pollack, 2020]. Therefore, this provides a unique therapeutic opportunity for ADP-A2M4 to potentially become the first licensed cell therapy product in post-1st-line advanced (inoperable)/metastatic synovial sarcoma if the overall benefit-risk findings from this phase 2 trial (study ADP-0044-002) are favorable.

3. OBJECTIVES AND ENDPOINTS

Objectives	End Points
Primary:	
To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review in Cohort 1
Secondary:	
To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	For Cohort 1 and across Cohorts (overall): • 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-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review across Cohorts (overall) For Cohort 1 and across Cohorts (overall): • Time to Response (TTR) • Duration of Response (DoR) • Best Overall Response (BOR) • Progression Free Survival (PFS) • Overall Survival (OS)

Development and validation of an in vitro diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Across Cohorts: • Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay
Characterize the in vivo cellular pharmacokinetics (PK) profile of ADP-A2M4 cells	For Cohort 1 and across Cohorts (overall): • Peak persistence and other relevant PK parameters of ADP-A2M4 cells
Exploratory	
[redacted]	[redacted] • [redacted] • [redacted] • [redacted] [redacted] • [redacted]
[redacted]	[redacted] • [redacted] • [redacted]
[redacted]	[redacted] • [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2 single arm, open label study of genetically engineered ADP-A2M4 in HLA-A*02 subjects with MAGE-A4 expressing metastatic or inoperable (advanced) synovial sarcoma or myxoid/round cell liposarcoma (Cohort 1 only). Only subjects with advanced synovial sarcoma will be eligible for Cohort 2. The study consists of two separate, independent, serially enrolled subject cohorts: Cohort 1 and Cohort 2.

Enrollment into Cohort 1 is expected to continue for approximately 12 months and is close to completion at the time of this amendment. Forty-five subjects have been enrolled and 26 subjects have been treated with ADP-A2M4 to date. Enrollment will continue to ensure that at least 45 subjects are dosed in Cohort 1. Dosing is expected to be complete in Cohort 1 in March 2021. Data from subjects in Cohort 1 only will be used for the primary study endpoint and primary statistical analysis.

The clinical and scientific rational for including Cohort 2 is to provide an expanded safety and efficacy data set overall in inoperable (advanced)/metastatic synovial sarcoma to supplement the primary assessment for Cohort 1 subjects who were previously enrolled in Cohort 1 may not enroll into Cohort 2.

4.1.1. Pre-screening

Subjects will sign a Pre-screening Informed Consent Form (ICF) and undergo initial screening for the relevant HLA 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 consent in accordance with IRB/IEC approved processes and any local requirements in advance of providing subjects with a HLA buccal/ cheek swab test and/ or sending tissue for MAGE-A4 testing.

4.1.2. Screening

Subjects who have pre-screened 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 the study. Screening assessments should be completed within 28 days of leukapheresis; CT/ MRI scans and ECHO/MUGA scans, performed as standard of care within 28 days prior to Screening Visit 2 (i.e. prior to treatment consent) are acceptable. Cytogenetic confirmation of diagnosis can be historic, done as standard of care, or be done any time after signing Treatment Consent and does not need to be within 28 day screening window.

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-A2M4 cell Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation.

Anticancer therapy may be administered between screening and leukapheresis, and between leukapheresis and the start of lymphodepletion (bridging therapy), if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods must be adhered to (see Section 5.3). Subjects must be ready to receive IP as the next treatment once manufacturing and any mandatory washout periods are complete even if they remain stable on bridging therapy, provided they have measurable disease per RECIST v1.1.

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

Once the ADP-A2M4 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5) (Section 6.2) followed by infusion of ADP-A2M4 cells on Day 1 (Section 6.3). The lymphodepleting chemotherapy may be given as an outpatient treatment or subjects may be hospitalized at the discretion of the Investigator. 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. 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.

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 local and independent review 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'), disease progression will not be determined before 4 weeks (28 days) post infusion of ADP-A2M4 unless there is unequivocal clinical evidence of deterioration. Therefore, imaging scans should not be performed earlier than 4 weeks (on or after 28 days) post infusion.

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 adverse events in accordance Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements for gene therapy clinical trials [FDA, 2006a; FDA, 2010; EMA, 2009].

Subjects will be seen in the clinic for evaluation according to Main T&E Table 1 (Section 1.3.1) until disease progression. Thereafter, subjects will undergo assessments/procedures according to the LTFU T&E Table 2 (Section 1.3.2). The timepoint at which the subject switches to the LTFU assessments/procedures will be driven by the timepoint at which the subject progresses e.g. if there is disease progression at Week 12, the next visit would be due at Week 24 (Month 6).

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

4.2. Scientific Rationale for Study Design

This is a Phase 2 single arm, open-label study with ADP-A2M4 cells for the treatment of subjects with advanced synovial sarcoma or MRCLS who are HLA-A*02 positive and have tumors that express MAGE-A4.

MAGE-A4 is a cancer testis antigen that is highly expressed in synovial sarcoma and MRCLS tumors making it an attractive target. Preliminary clinical evidence in Study ADP-0044-001 has shown an ORR (confirmed responses) of 44% (95% CI: 16.34, 67.71) in advanced (inoperable)/metatstatic synovial sarcoma with a disease control rate of 94% including 11 out of 16 patients who were still alive at time of 1-September-2020 data cut-off. Synovial sarcoma responses were durable with a median duration of response of 28 weeks (range: 12-72 weeks). [CTOS 2020]. This ORR is considerably superior than response rates reported with agents currently being used as 2nd line therapies for soft tissue sarcoma (Section 2.2.3).

On this basis, this Phase 2 study (ADP-0044-002) will be a single arm, non-comparative study with a primary efficacy endpoint of Overall Response Rate (ORR) per RECIST v1.1 by independent review in 2 Cohorts where the primary study endpoint will be evaluated in Cohort 1. The historical ORR for post first-line metastatic soft-tissue sarcoma patient populations ranges from 4%-13% (Section 2.2.3). To account for the potential variability in historical control response rate, a more conservative historical ORR of 18% has been estimated for therapies administered in the post 1st-line metastatic synovial sarcoma setting, and will be used to evaluate the efficacy of ADP-A2M4 by hypothesis testing (Section 9).

At the time of this Protocol Amendment (05FEB2021) the ADP-0044-002 study has been enrolling subjects for approximately 12 months. Fifty-three subjects have been enrolled, and 31 subjects have received treatment with a single dose of ADP-A2M4 in Cohort 1 including 27 subjects with advanced (inoperable)/metatstatic synovial sarcoma and 4 subjects with MRCLS.

[redacted]

The clinical and scientific rationale for including Cohort 2 is to provide an expanded safety and efficacy dataset overall for metastatic or inoperable (advanced) synovial sarcoma to supplement the primary assessment for Cohort 1.

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 of HLA-A*02:01, HLA-A*02:03 or HLA-A*02:06. HLA-A*02 alleles having the same protein sequence as these alleles in the antigen binding domains (P group) will also be included. 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.

Due to the risk of alloreactivity subjects positive for HLA-A*02:05 in either allele are ineligible. Subjects with HLA-A*02 alleles having the same protein sequence as HLA-A*02:05 in the antigen binding domains (P groups) will also be excluded. Other alleles may be exclusionary after consultation with the sponsor. HLA eligibility testing will be done via Adaptimmune designated central laboratory.

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 high proportion of subjects expected to be excluded based on HLA status, an optional buccal swab kit may be offered to subjects during pre-screening 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 associated instructions would be sent to potential subjects who have provided written 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 screening.

4.2.1.2. MAGE-A4 Expression in Tumor

MAGE-A4 expression was reported in synovial sarcoma (82%) and myxoid liposarcoma (68%) cases [Iura, 2017a; Iura, 2017b]. ADP-A2M4 cells have been shown to produce strong IFNγ responses against tumor cell lines (derived from non-small cell lung cancer, prostate carcinoma, melanoma and ovarian carcinoma) expressing high MAGE-A4 mRNA levels (>10,000 MAGE-A4 transcripts). In addition, ADP-A2M4 cells elicited a strong IFNγ response against a primary melanoma tissue material expressing high MAGE-A4 mRNA and protein expression levels. Since no adequate models to define the threshold of ADP-A2M4 cell activation are currently available, this protocol will select for subjects with high MAGE-A4 expression. As such, Adaptimmune will be using a conservative cutoff (≥2+ in ≥ 30% of tumor cells) to ensure sufficient expression of the antigen.

To ensure that the subject's tumor has the potential to be targeted by the ADP-A2M4 cells, the tumor specimen will be screened at a central reference laboratory for the expression of MAGE-A4 by IHC using a Clinical Laboratory Improvement Amendments (CLIA)-validated Clinical Trial Assay.

4.2.2. T Cell Manufacturing

ADP-A2M4 is autologous CD4 and CD8 T cells engineered with an affinity-enhanced TCR to target the tumor antigen MAGE-A4. Autologous T cells are obtained from eligible subjects who have MAGE-A4 positive tumors and who have appropriate HLA-A. The CD4 and CD8 T cells are transduced with a SIN lentivirus vector expressing the MAGE-A4 (affinity enhanced clone 1032) under GMP conditions. The product of this transduction is polyclonal T cells which are designed to target MAGE-A4 in tissue. The transfer SIN lentiviral vector has been meticulously designed to contain the genetic elements required for function and for maximum biosafety [Dull, 1998]. Many reports provide evidence supporting the relative biosafety of SIN lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the lentivirus long terminal repeat (LTR) in comparison to the γ retroviral vectors [Montini, 2006; Maruggi, 2009; Modlich, 2009; Montini, 2009].

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

4.2.3. Lymphodepletion

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

Evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia and acute leukemia using adoptive cellular therapy including a CAR showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in a previously cyclophosphamide-only preparative regimen [Turtle, 2015]. Cyclophosphamide was administered at 30 – 60 mg/kg x 1 day and fludarabine at 25 mg/m^2/day x 3 – 5 days. Effective lymphodepletion has also been demonstrated in other CAR-T cell studies using reduced cyclophosphamide dosing, together with fludarabine [Batlevi, 2016].

Data from an open label non-randomized multi-cohort pilot study of genetically engineered NY-ESO-1 SPEAR™ T cells in HLA-A2+ patients with synovial sarcoma (NCT01343043) suggests that fludarabine is an important component of T-cell lymphodepleting regimens and fludarabine 30 mg/m^2 given daily for 4 days in combination with cyclophosphamide may be associated with more objective responses [D'Angelo, 2018] (see Section 2.2.3). The CD19 CAR-T product tisagenlecleucel also utilizes fludarabine 30 mg/m^2 for 4 days in combination with cyclophosphamide.

The lymphodepleting regimen in this study consists of intravenous fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5).

4.2.4. Long Term Follow-up

Subjects exposed to gene therapies may be at risk for delayed adverse events 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 long term follow up (LTFU) evaluation in the study is designed to adhere to the FDA and EMA guidance for long term follow up of subjects in gene therapy clinical trials [FDA, 2006a; FDA, 2006b; FDA, 2010; EMA, 2009], and involves monitoring subjects who have been exposed to lentivirus-mediated gene transfer in this clinical study for 15 years. Further information on safety monitoring for theoretical risks associated with the use of lentiviral vectors and potential for insertional oncogenesis, as well as safety monitoring are available in Section 10.7, Appendix 7.

4.3. Justification for Dose

The cell dose of ADP-A2M4 is within the range of 1×10^9 to 10×10^9 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 or an additional leukapheresis collection may be 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-A2M4 is being assessed in a Phase 1 trial of multiple tumor types including synovial sarcoma and MRCLS (NCT03132922). Doses up to 9.96 x 10^9 have been well tolerated in this Phase 1 dose escalation study and was associated with a high ORR in 16 advanced (inoperable)/metastatic synovial sarcoma subjects [CTOS 2020].

4.4. End of Study Definition

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

5. STUDY POPULATION

5.1. HLA and Antigen Pre-screening

To be eligible for Pre-screening (Visit 1) subjects must be aged ≥16 and ≤75 years with a diagnosis of advanced (metastatic or inoperable) synovial sarcoma (Cohort 1 or Cohort 2) or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by either histology or cytogenetics. Confirmation of diagnosis by cytogenetics is required prior to leukapheresis.

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 all of the following criteria prior to leukapheresis (i.e. at Screening (Visit 2)) AND prior to lymphodepleting chemotherapy (i.e. at Baseline) to be eligible to participate in this study.

1. Subject (or legally authorized representative) voluntarily agrees to participate by giving written informed consent (and Assent as applicable) in accordance with ICH GCP guidelines and applicable local regulations.
2. Subject (or legally authorized representative) agrees to abide by all protocol required procedures including study related assessments, and management by the treating institution for the duration of the study including long term follow-up.
3. Age ≥16 and ≤75 years at the time the Pre-screening Informed Consent/Assent is signed.
4. Diagnosis of advanced (metastatic or inoperable) synovial sarcoma or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by cytogenetics. Inoperable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise.
    a. For Synovial Sarcoma (Cohort 1 and Cohort 2): confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)).
    b. For MRCLS (Cohort 1 only): confirmation by the presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) or t(12; 22) (q13;q12).
5. Must have previously received either an anthracycline or ifosfamide containing regimen. 1st-line metastatic treatment with ADP-A2M4 is permissible if ifosamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumour setting.(Subjects who are intolerant of both anthracycline and ifosfamide must have previously received at least one other type of systemic therapy).
6. Measurable disease according to RECIST v1.1.

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 as these alleles in the peptide binding domains (P group) will also be included. Other HLA-A*02 alleles may be eligible after adjudication with the sponsor.
8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥2+ staining in ≥30% of the cells by immunohistochemistry. 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%.
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 an 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 a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide).
13. Must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support) within 7 days prior to lymphodepletion and leukapheresis
Platelets	≥ 100 x10^9/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)
Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)

Coagulation	
Prothrombin Time or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation. Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Renal	
Glomerular filtration rate (calculated CrCl using only the Cockcroft-Gault equation, or measured using either a 24-hr urine creatnine collection or a radionuclide EDTA test) [1]	≥ 60 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)
Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT)	≤ 2.5x ULN
[1] 24-hour urine creatine clearance or radionuclide EDTA tests should be used to measure the GFR in all subjects: ≥ 65 years old; clinically obese (≥ 30KG/m^2) or	

underweight (≤18.5KG/m^2); borderline low calculated CrCl (Cockcroft-Gault) at approximately 60mls/min. (see Section 8.4.10 for further details).

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

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
Tyrosine kinase inhibitor (TKI) (e.g. pazopanib)	1 week	1 week
Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors,)	4 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 week 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	Subjects who have received a gene therapy using any DNA-integrating vector other than a lentivirus (retrovirus, AAV, etc.) are excluded from this study. Subjects who have received a gene therapy using a lentiviral vector may	Not permitted after leukapheresis and prior to lymphodepletion.

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
	be eligible if they have persistence results below the lower limit of quantification (LLOQ) for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.	
Corticosteroids or any other immunosuppressive therapy. NOTE: Use of topical steroids is not an exclusion. See Section 6.5.1 for exceptions.	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 washout period for palliative radiation to non-target organs).
Major surgery	N/A	4 weeks. A subject must be fully recovered from any surgical 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, 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. Symptomatic CNS metastases including leptomenigeal disease. Subject with a prior history of symptomatic CNS metastasis including leptomenigeal disease must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiation (WBRT) and/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.
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;
    - Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4;
    - Uncontrolled clinically significant arrhythmia;
    - Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months;
    - Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent);
    - Congenital or family history of long QT syndrome;
    - Current uncontrolled hypertension despite optimal medical therapy;
    - History of stroke or central nervous system bleeding; transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) in last 6 months;
    - Incipient compression/occlusion of a vital structure (e.g. bronchus; superior vena cava; renal outflow tract) which cannot undergo prophylactic stenting;

- COVID-19 infection or a positive COVID-19 RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy. If a subject has a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart.

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 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

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.

5.5. Number of Subjects and Study Duration

Forty-five (45) subjects (90 total subjects) are planned to be dosed separately in both Cohort 1 (synovial sarcoma and MRCLS) and Cohort 2 (synovial sarcoma only). In combination, data from Cohort 1 and Cohort 2 will provide a better, more comprehensive, characterization of the benefit-risk profile in soft-tissue sarcoma patients (especially in synovial sarcoma) than from Cohort 1 alone.

Enrollment into Cohort 1 is expected to continue for approximately 12 months and is close to completion at the time of this amendment. Cohort 2 will begin when dosing in Cohort 1 is completed. Cohort 2 will dose 45 advanced (inoperable)/metastatic synovial sarcoma subjects only and enrollment is expected to continue for approximately 12 months. The Primary Clinical Analysis will be for Cohort 1 only (i.e. synovial sarcoma plus MRCLS). Clinical cut-off for the

primary analysis will occur once the last subject dosed in Cohort 1 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 from Cohort 1 only 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 the study for any reason.

5.6. Sites

The study will be conducted in approximately 24 sites in North America and Europe. The number of centers is necessary to ensure recruitment in this rare patient population. Additional sites may be added at the discretion of the Sponsor.

6. STUDY INTERVENTION

6.1. Leukapheresis

Subjects who complete screening procedures defined in 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-A2M4.

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

A non-mobilized peripheral blood mononuclear cell (PBMC) collection should be performed by an apheresis unit at the enrolling institution according to the institution's or hospital's policies and procedures. Leukapheresis may be performed at a qualified third-party institution (as may be mutually agreed and approved in advance by both Sponsor and the clinical site), as long as the policies and procedures in place meet or exceed the primary institution's policies and procedures. Bilateral peripheral venous access should be used whenever possible but a temporary central venous catheter (CVC) may be placed for collection if peripheral venous access is inadequate. Standard clinical procedures for apheresis should be followed.

A large volume leukapheresis should be performed. For subjects who are >50 kg, 10 to 15 liters should be processed per procedure; in subjects ≤ 50kg, 2-3 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 calcium chloride and magnesium sulfate 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, may be used by the sponsor for research to modify or improve the manufacturing process and to enhance the clinical response.

6.2. Lymphodepleting Chemotherapy

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

Once the manufactured ADP-A2M4 cell product has been received at the clinical site and the integrity of the bag(s) has been verified by the site, eligible subjects will proceed to have lymphodepleting chemotherapy with fludarabine and cyclophosphamide as described in Table 3.

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 prophylaxis (see Section 10.5.3.7) in line with institutional guidelines.

Appropriate intravenous (IV) hydration should be administered and Mesna should be given to prevent urotoxicity while cyclophosphamide is administered, as described below. Other premedication (e.g. anti-emetics) may also be provided in accordance with institutional standards. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. Based on real-world use of Granulocyte-colony stimulating factor (G-CSF) prophylaxis in Cohort 1 at the study sites, especially those with extensive CD19 CAR-T cell therapy expertise, G-CSF prophylaxis in Cohort 2 synovial sarcoma subjects can be given at the clinical discretion of the Investigator (as per local instituitional policy) starting on Day -3 until resolution of neutropenia in accordance with American Society of Clinical Oncology (ASCO) guidelines or institutional practice (see Section 6.2.3).

Table 3: Fludarabine and Cyclophosphamide Treatment Schema

Lymphodepleting Chemotherapy				
Day	**Drug**	**Dose**	**Route**	**Administration**
-7	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[3]
-6	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[3]
-5	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[2]
-4	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
-3	**Start G-CSF**[4]			
-2				
-1				
1	**ADP-A2M4 infusion**[3]			

[1] Fludarabine dose will be adjusted for renal impairment as described in Section 6.2.1
[2] Concentration of 1mg/ml or less
[3] Administration of ADP-A2M4 infusion is described in Section 6.3.
[4] Administration of G-CSF 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
60 – 79 mL/min	20 mg/m^2

Renal function should be estimated using the Cockcroft-Gault Creatnine Clearance (CrCl) equation (no other renal function equations are permitted).

A more sensitive evaluation of renal function using either a 24-hr urine creatinine collection or a EDTA radionuclide test should be performed in subjects at Screening and/or Baseline who are:

- Obese (i.e. BMI ≥ 30 KG/m2
- Underweight (i.e. BMI < 18.5 KG/m2)
- Low borderline CockCroft-Gault calculated CrCl of approximately 60 ml/min.

6.2.2. Mesna

Mesna should be administered according to institutional practice or as recommended below:

- 120 mg/m^2 (20% cyclophosphamide dose) as an IV bolus pre infusion, 4 and 8 hours post infusion on each day of cyclophosphamide administration.

6.2.3. G-CSF

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

6.3. Investigational Product

6.3.1. Premedication

Subjects will be premedicated with antihistamine and acetaminophen/paracetamol 30-60 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.

6.3.2. T Cell Infusion

On Day 1, the subject will receive thawed ADP-A2M4 by intravenous infusion. The T cell infusion will be given as an inpatient procedure and subjects will remain hospitalized for observation for at least 24 hours post T cell infusion.

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

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

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

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

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

If after thawing the infusion bag is damaged or leaking, the 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 15-45 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 - 250 ml of 0.9% sodium chloride should be connected to the second lumen of the infusion set, used to prime the line, and then the lumen closed. On completion of the infusion of a bag of T-cell product, the main line should be closed and approximately 50ml saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided.

On completion of the cell infusion the set should be flushed using additional saline from the attached bag. If Institutional practice requires a single spike infusion set (e.g. macro drip IV tubing) standard institutional guidelines for the infusion of autologous cell infusion should be followed. The line must be flushed with 0.9% sodium chloride once the infusion is complete. In the event of adverse reaction to the cell infusion the infusion rate should be reduced and the reaction managed according to institutional standard procedures. Steroid treatment should be avoided unless medically required.

In the event a subject develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia (see Section10.5.3).

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.

6.4. Preparation/Handling/Storage/Accountability

6.4.1. Packaging and Labelling

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

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

6.4.2. Receipt and Return

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

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

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 investigational product 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 Investigational Product are correctly received by a responsible person
- Such deliveries are recorded
- Investigational product is handled and stored safely and properly as instructed in the Apheresis and T cell Product Manual
- Investigational product is only administered to study subjects in accordance with the protocol
- Investigational product administration is documented. Records must include the identification of the person to whom the investigational product 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 investigational product 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 investigational product in the trial will be provided with an alert card, which has been previously agreed by the sponsor and approved by the institutional review board (IRB)/ independent ethics committee (IEC). Alert cards will contain at a minimum the name of the subject, the investigator contact number and information regarding the investigational product 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 anticancer locoregional therapies such as non-palliative radiation.

Subjects who undergo any active anticancer therapy, with the exception of surgical resection prior to disease progression, will be considered as having met the 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 ADP-A2M4. However, a subject whose tumor becomes resectable and who undergoes surgical resection prior to disease progression, will continue to be followed for safety and efficacy (progression of remaining lesions, new lesions) in the interventional phase of the study until disease progression is determined. Upon progression, the subject will follow the LTFU schedule. Subjects who have surgery for new lesions consistent with progressive disease or to control progressive disease in previously identified lesions will discontinue the interventional phase and follow the LTFU schedule.

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

The use of systemic steroids may abrogate the effects of the T-cell therapy and therefore use is discouraged unless required to manage CRS (see Section 10.5.6 for CRS treatment recommendations) or other significant immune-mediated adverse events. According to local standard of care or ASCO guidelines, steroids may be used as antiemetics 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. 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 and record the disease progression in the eCRF.

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

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

- All prescription and nonprescription medication, vitamins, herbal and nutritional supplements taken by the subject during the 30 days prior to screening (Visit 2) will be recorded at the screening visit.
- All prior anti-cancer treatments taken by the subject must be recorded regardless of time frame taken
- All concomitant medications taken while subjects are in the interventional phase

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 Immunocompromised 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-A2M4 cell infusion, should be discussed with the Medical Monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Temporary Study Suspension

Throughout the conduct of the study, safety data will be reviewed on an ongoing basis by a Data Safety Monitoring Board (DSMB) see Section 10.2.1. If the following events occur, further enrollment to the study will be suspended and the regulatory authorities informed:

- A subject has a positive RCL:
  - Confirmed positive peripheral blood mononuclear cell (PBMC) replication competent lentivirus (RCL) and no other vector lot is available for use in transduction for subsequent subjects (refer to Section 10.7.2 and Figure 1 on monitoring and management of RCL)
  - Confirmed biological RCL - all ADP-A2M4 cell infusions are halted (see 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
- Died
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- Adverse Event
- Lost to follow-up
- Pregnancy (see Section 10.6.2.1)
- Termination of enrollment by the Sponsor

All subjects ending the interventional phase, with the exception of those who withdraw consent, die, are unable/unwilling to comply with study requirements, are lost to follow up or did not receive any T cells, will switch to the LTFU schedule Table 2, Section 1.3.2 to continue observation for delayed adverse events 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 whole 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 withdrawal of a subject from the study are:

- Unable/Unwilling to comply with study requirements
- Adverse event
- Withdrawal of consent
- Investigator decision
- Lost to follow-up (see Section 7.4)
- Study termination by 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

8.1. Background Assessments

8.1.1. Demographics

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

8.1.2. Disease History

The following information will be recorded in the eCRF: date of initial diagnosis, primary tumor type, anatomical site and size of primary tumor, histology, last known stage of disease and chromosomal translocations.

8.2. HLA MAGE-A4 Tumor Antigen Testing, and Cytogenetics

There is no window for obtaining HLA, MAGE-A4 antigen and cytogenetic testing 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 approved HLA Sequencing System for Sequence Based Typing (SBT) of Human Leukocyte Antigen (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 subjects' 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 study Sample Collection 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 Sample Collection 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.

8.2.3. Cytogenetics for Diagnosis

For Synovial Sarcoma (Cohort 1 and Cohort 2), a confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)) is required prior to leukapheresis

For MRCLS (Cohort 1 only), a confirmation by the presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) or t(12; 22) (q13;q12) is required prior to leukapheresis.

Cytogenetic confirmation of diagnosis can be historic, done as standard of care, or be done any time after signing the Treatment ICF and does not need to be within the 28 day screening window.

8.3. Efficacy Assessments

8.3.1. CT/MRI

Imaging scans of the chest, abdomen and pelvis should be performed at Screening, 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 independent review, scheduled study 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 8.4.9 regarding brain MRI for safety assessment.

Acceptable imaging modalities for this study include:

- 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 a non-contrast enhanced CT of the chest, if contrast enhanced CT is contraindicated for a subject
- MRI of the extremities if clinically indicated.
- 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 inflammation'), disease progression will not be determined before 4 weeks post infusion of ADP-A2M4, 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 not 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-A2M4 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 patient care throughout the study.

8.3.2. Survival

If a subject dies during the study date of death will be recorded in the eCRF. 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 Test in Table 4 describe 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 four 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) in the subject's eCRF.

8.4.2. Physical Examination

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

8.4.3. Prior Anti-cancer Therapies

All 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 recorded on the concomitant medication page of the CRF 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 Section 10.9, Appendix 8 for guidance. It is recommended, where possible, that a subject's ECOG be assessed by the same person throughout the study. The frequency of the ECOG assessment is specified in Table 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 only once at Baseline. Weight will be measured according to the frequency specified in Table 1.

8.4.8. Cardiac Assessments

Cardiac assessments will be performed locally at the site.

8.4.8.1. ECG

A single ECG is required. Heart rate, rhythm, PR, RR (if measured/recorded), QRS and QTc intervals will be recorded. QTcB or QTcF is acceptable as per institutional standards but must be consistent from visit to visit.

For Screening (Visit 2) ECGs performed as standard of care within 28 days prior the visit are acceptable. The ECG on Day 1 will taken before T cell infusion starts.

8.4.8.2. Echo/MUGA

An ECHO or MUGA scan will be performed at screening to determine left ventricular ejection fraction (LVEF) for eligibility. ECHO/MUGA scans performed as standard of care within four 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.

8.4.8.3. Telemetry

For subjects with known cardiac or pericardial tumor involvement at baseline, inpatient telemetry monitoring should be carried out for seven days post-ADP-A2M4 infusion.

8.4.9. Brain MRI

A MRI of the brain with contrast will be obtained at Baseline, within 1 month of lymphodepletion, for all subjects. CT with IV contrast may be used only for subjects with contraindications to MRI of the 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 (see Section 8.3.1). If brain metastases are not documented at Baseline, then dedicated brain CT/MRI scans should be performed as clinically indicated.

8.4.10. Renal Function Assessment

Renal function (estimated or measured glomerular filtration rate (GFR)) will be assessed at Screening using the Cockcroft-Gault CrCl equation. 24 hour urine collection to measure creatinine clearance or by nuclear medicine EDTA measurement should be performed in subjects who are i). clinically obese (i.e. $\geq$ 30KG/m^2); ii). clinically underweight (i.e. $\leq$ 18.5KG/m^2); iii). $\geq$ 65 years old; iv). Low borderline calculated CrCl ~ 60 ml/min (Cockcroft-Gault).

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

8.4.11. Hematology

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

In years 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 8.4.22) then laboratory assessments may be discontinued.

8.4.12. Clinical Chemistry

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

In years 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 8.4.22) then laboratory assessments are discontinued.

8.4.13. Coagulation

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

Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.

8.4.14. Thyroid Function Tests

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

8.4.15. 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 (see Appendix 4, Section 10.4.5).

8.4.16. Pregnancy Test

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

8.4.17. 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 six 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.

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

8.4.18. CMV PCR

Subjects will be screened for cytomegalovirus (CMV) seropositivity at screening. If seropositive at screening, then CMV-PCR will be done at Baseline. 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, week 2, 4, 6, and 8. See Section 10.5.3.4 for CMV prophylaxis and blood product screening if positive.

8.4.19. ICE Assessment Tool

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

If a subject is thought to have ICANS, the ICE should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated. See Section 10.5.7, Table 7.

8.4.20. C-reactive Protein

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

8.4.21. Ferritin

If cytokine release syndrome is suspected, ferritin levels should be measured approximately every other day with C-reactive protein.

8.4.22. 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 8.6.5).

Samples are required for:

- Safety at Baseline and Week 24, Month 12 and then every 6 months through Year 5 and annually from Years 6-15.
    - 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 may be discontinued.
    - 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 (Appendix 6 Section 10.7.3).
- Research at Day 2, Day 4, Day 8, Week, 2, Week 4, Week 8, Week 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 Sample Collection Manual.

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

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

If a positive VSV-G DNA signal is obtained, the study investigator will be informed and the subject will be scheduled for a retest as soon as possible and no later than one month after the initial positive result was reported to the Sponsor. See Appendix 7 Section 10.7.2 for additional information.

Details on collection and shipment of blood sample for RCL is described in the Sample Collection 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, tumor biopsy) until 24 hours afterwards for blood sampling, or until 2 weeks post-biopsy.
- From date of signing the Treatment ICF 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 discontinues the interventional phase of the study. In addition, emerging clinical conditions defined in Appendix 4, Section 10.4.6 will be monitored for starting Day 1. If the subject has not progressed after 12 months, only those emerging clinical conditions defined in Appendix 4, Section 10.4.6 will be collected thereafter.
- During the long-term follow-up phase of the study, subjects will only be monitored for the emerging clinical conditions defined in Appendix 4, 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 Appendix 4.

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.

8.5.2. Method of Detecting Aes and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4, 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 participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All Aes and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 4, Section 10.4.3.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt (within 24 hours) notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (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 in the form of Investigator Safety Letters (ISL).
- An investigator who receives an investigator safety letter describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and 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 which 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 investigational product. Details of all pregnancies in female participants and female partners of male participants will be collected from the start of lymphodepletion for as long as there is evidence of T-cell persistence, or until the subject has confirmed disease progression.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6. See Section 10.6.2 for guidance.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

The safety of ADP-A2M4 during pregnancy and lactation has not been established in humans. The target antigen is known to be expressed on fetal germ line tissues and placenta, therefore female subjects who are pregnant, intending to become pregnant, or breast feeding are excluded from ADP-A2M4 studies.

There is no preclinical or clinical trial data of ADP-A2M4 in pregnant women; however, there is a reasonable but unproven likelihood that this intervention may be significantly embryotoxic or even an abortifacient given the underlying biology of the target. The effects on breast milk are unknown, therefore breastfeeding should be discontinued for the duration of the study, starting at the first dose of chemotherapy and for at least 12 months after receiving the investigational product, or four months after there is no evidence of persistence/gene modified cells in the Subjects blood, whichever is longer.

The contraception guidelines provided in Section 10.6.1 should continue to be adhered to during long-term follow up.

A woman who becomes and remains pregnant during the study will be discontinued from the-interventional phase as exposure to radiation from imaging studies would be contraindicated. The subject would follow the LTFU T & E schedule 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

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 which 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 seven 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.

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 grading and management of CRS.

8.5.7.2. Neurotoxicity

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 cytokine release syndrome (CRS) symptoms. This form of ICANS tends to be of shorter duration, lower grade (Grade 1–2, see 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 CART-cell therapy, after the initial fever and CRS subside [Lee, 2019].

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

8.5.7.2.1. Monitoring for ICANS

The ICE is a neurological assessment tool which is used to assess cognitive function to monitor for ICANS (see Section 10.5.7 for details). ICE should be measured on the day of ADP-A2M4 infusion prior to receiving treatment and through Day 8 whilst the subject is hospitalized. If the subject is discharged before Day 8 the ICE may be discontinued according to the T&E Table (Section 1.3.1). Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following ADP-A2M4 infusion if hospitalized. If a subject is found to have ICANS, the ICE 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. ICE also forms part of the grading system for ICANS developed by [Lee, 2019].

ICANS is graded and managed according to the severity of symptoms, see Section 10.5.7.1 for detailed guidance on management of ICANS.

8.5.8. Long Term Follow Up Adverse Events

During the long term follow-up (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 Letters 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 (Appendix 7, 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 T&E Table (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]

[redacted]

- [redacted]
- [redacted]

[redacted]

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

- [redacted]
- [redacted]

[redacted]

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

[redacted]

- [redacted]
- [redacted]

8.6.1. Tumor Biopsy

Baseline biopsy material should be collected within two months of the T cell infusion, with preference for a biopsy to be taken closer to the time of infusion. Tumor tissue should either be taken from non-target lesions or from target lesions where sampling can be done without 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).

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 collected obtained post-progression (e.g. from an excisional surgery).

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

8.6.2. Cytokine and Soluble Protein Analysis

Serum is collected at Baseline, pre-infusion and 2-4 hours post infusion on Day 1 and on Day 2, Day 4, Day 8, Week 2, 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 Sample Collection Manual.

Serum samples may also be used to detect humoral immune responses to tumor antigens and antibodies to ADP-A2M4.

8.6.3. [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

8.6.4. [redacted]

[redacted]

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

8.6.5. Persistence of ADP-A2M4 TCR$^+$ 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 8.4.22. 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]

- [redacted]

8.7. Patient-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, 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 (VAS) 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 Month 12. Once disease progression is established, the EQ-5D-3L assessment is no longer required.

8.7.2. EORTC-QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed by the Quality of Life Group of the European Organisation for Research and Treatment of Cancer to assess the quality of life of cancer patients.

The EORTC QLQ-C30 will only be used in synovial sarcoma subjects in Cohort 2 at Baseline and post T-cell infusion at Week 8, Week 16, Week 24 and Month 12. Once disease progression is established, the EORTC QLQ-C30 assessment will no longer be required.

The EORTC QLQ-C30 comprises 30 questions. Each of the first 27 questions has 4 levels: Not at All, A Little, Quite a Bit, and Very Much. The respondent is asked to indicate his/her health state by selecting the most appropriate statement. Questions 29 and 30 records the respondent's self-rated health on a horizontal scale where the endpoints are labelled 'Very Poor' and 'Excellent'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

9. STATISTICAL CONSIDERATIONS

The objectives and endpoints for this study are described in Section 3, this section focusses on key aspects for 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). The analysis plan for the objective related to the development of the validated Companion Diagnostic (CDx) will be described in a separate document. Similarly, 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.

The primary analysis will be for Cohort 1 only 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-A2M4) in Cohort 1.

The primary endpoint for efficacy is Overall Response Rate (ORR) in Cohort 1, defined as the proportion of subjects with a confirmed CR or PR relative to the total number of subjects in the analysis population.

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

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

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

- The historical ORR for Synovial Sarcoma ≤13% and for MRCLS <10% (Section 4.2)
- The ORR for historical control that will be used for hypothesis testing in this study will be 18%.
- The mechanism of action for the TCR is assumed to be the same for synovial sarcoma and MRCLS.
- Section 2.2.3 states that in subjects with synovial sarcoma, the observed ORR (confirmed responses) for ADP-A2M4 cell therapy was 40.0% at the time of data cut off. Therefore,

for purposes of sample size computation, we assumed ORR for ADP-A2M4 cell therapy would be 40%.

- No formal hypothesis testing is planned for Cohort 2 or across cohorts (overall).

The hypothesis of interest for the primary endpoint is;

(Null Hypothesis) H_0: $p \leq p_0$, vs. (Alternate Hypothesis) H_1: $p > p_0$, where p_0 (historical control rate) = 0.18.

Based on above assumptions, the TCR ORR (i.e., p_1) is set at 0.4. The type I error (α) for this test will be no more than 0.025 and the type II error (β) will not exceed 0.1. Exact Binomial methods will be used to test the hypothesis.

Statistical Design Assumptions:

- The assessment for efficacy will be based on the mITT population using confirmed ORR via RECIST v1.1 per independent review in Cohort 1;
- The type I error (α) for this test will be no more than 0.025;
- The type II error (β) will not exceed 0.1;
- Exact Binomial method will be used to test the hypothesis;
- Cohorts 1 and 2 are independent.

Based on the statistical design assumptions above and the hypotheses and clinical assumptions in Section 4.2, the estimated sample size for the trial is 45 subjects in Cohort 1)

The ORR for Synovial Sarcoma ranges between 4% – 13% in clinical trials (Section 2.2.3). If we assume that the ORR of the ADP-A2M4 will be 40% (P1), and historical ORR (P0) is 13%, a sample size of N=27 provides 90% power to detect an absolute difference of 27% using exact binomial assumptions.

To account for the potential variability in historical control efficacy, a more conservative historical ORR of 18% may also be considered. Using a one-sided alpha=0.025, if we assume that the ORR of ADP-A2M4 will be 40% (P1) and historical ORR may be as high as 18% (P0), a sample size of N=45 in Cohort 1 provides at least 90% power to detect a difference of 22% using exact binomial assumptions.

The following table describes samples sizes for a single cohort under a range of assumptions for the exact binomial assumption as described above.

Historical ORR (P0)	TCR ORR (P1)	Difference (P1-P0)	N
0.13	0.40	0.27	27
0.13	0.45	0.32	21
0.15	0.40	0.25	33
0.15	0.45	0.30	24
0.15	0.50	0.35	19
0.18	0.40	0.22	45
0.18	0.45	0.27	32
0.18	0.50	0.32	21

Based on these evaluations, the sample size is 45 subjects in Cohort 1 for the primary analysis.

Additional subjects are enrolled in Cohort 2 to supplement Cohort 1 with additional safety and efficacy data based on clinical judgement. No formal hypothesis testing is planned for either Cohort 2 or overall. One benefit of these additional subjects is an increase in precision for ORR by assessing the endpoint across cohorts, and thus in a larger sample of subjects. The following table summarizes the width (point estimate – lower bound) of a 97.5% one-sided confidence interval using exact binomial methods for different sizes of Cohort 2. Also provided for context is the probability that the lower bound of the confidence interval exceeds p0=18% for different sizes for Cohort 2. The assumed TCR ORR is 40%.

Size of Cohort 2	Size of Overall (across cohort)	CI Width	Probability CI LB > 0.18
0	45	0.143	0.916
15	60	0.124	0.959
30	75	0.111	0.989
45	90	0.102	0.994

Based on these evaluations, enrolling an additional 45 subjects in Cohort 2 reduces the width of the confidence interval by about 28% [(0.143-0.102)/0.143] compared to the expected confidence interval width when only using Cohort 1. Further, if the TCR ORR is 40% the probability that the lower bound of the confidence interval exceeds 18% increases from about 92% when only using Cohort 1 subjects to greater than 99% if 45 subjects are enrolled in Cohort 2. These results support enrolling an additional 45 subjects in Cohort 2, for a total of 90 subjects aross cohorts.

9.3. Statistical Analyses

The statistical analysis plan (SAP) document will provide full details about data derivations and displays and analysis methods for primary, secondary and exploratory endpoints. This section captures key aspects of the analysis.

Demography and baseline characteristics will be summarized using appropriate descriptive statistics. Subject disposition including number of subjects leukapheresed, lymphodepleted and treated with ADP-A2M4 will be summarized. Reasons for subject discontinuation from the study will be displayed.

9.3.1. Interim Analysis

There is no interim analysis planned.

9.3.2. Efficacy Analyses

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

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

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).

The primary endpoint, ORR per RECIST v1.1 by independent review in Cohort 1, will be evaluated using a one-sided exact-based Clopper-Pearson 97.5% confidence interval (CI). If the lower bound of the 97.5% CI exceeds 18%, the trial has met the pre-specified threshold for demonstrating efficacy and the trial has met the criterion for statistical significance.

As a sensitivity analysis, one-sided 97.5% confidence interval using the Wilson method may also be provided.

ORR per RECIST v1.1 by independent review will also be evaluated across cohorts (overall).

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.

- Duration of Response (DoR), defined as the duration from the initial date of the confirmed response to the date of progressive disease or death.
- Progression Free Survival (PFS), defined as the interval between the date T-cell infusion and the earliest date of disease progression based on RECIST v1.1 or death due to any cause.
- Overall Survival (OS), defined 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 DoR and PFS. As a sensitivity analysis, determination of progression (via RECIST v1.1) using lesion assessments will also be provided.

All secondary efficacy endpoints will be summarized for Cohort 1 and across cohorts (overall).

No hypothesis testing is planned for these secondary endpoints in Cohort 1 or across cohorts. Time to event endpoints (i.e., 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. Two-sided 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.

The following censoring rules will be applied:

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

The proportion of censored observations will be summarized.

The pharmacokinetic (PK) profile 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.

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 also include the per protocol (PP) population. All safety analyses will be summarized for Cohort 1 and across cohorts (overall).

The safety profile will be based on adverse events, serious adverse events, replication competent lentivirus (RCL) and vector integration/clonality. 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.

Adverse events will be summarized using two time periods:

- From the time of signing the treatment ICF;

- From start of lymphodepleting chemotherapy, defined as starting on the first day of lymphodepleting chemotherapy.

Adverse events throughout the trial will be coded by MedDRA v21.0 or higher. The number and percent of subjects reporting any adverse events will be tabulated by system organ class and preferred term. Adverse events 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., cytokine release syndrome (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 electronic Case Report Form (eCRF). Within the EDC system the eCRF data will be entered by the site staff and all source document verification and data cleaning will be performed by the Sponsor or designee (e.g. CRO).

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

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

Standard coding dictionaries, WHO Drug and MedDRA will be used to code medications and adverse events.

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

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

10.1.1.2. Case Report Forms

For each subject enrolled, the completed eCRF must be reviewed and signed by the Principal Investigator or authorized delegate. If a subject discontinues 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, investigational product handling and accountability, presence of required documents, the informed consent process and comparison of eCRFs with source documents.

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

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

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

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and any other site level committee deemed appropriate by the Institution. Approval from each applicable committee will be received in writing before initiation of the study.

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

10.1.3.3. Local regulations/Declaration of Helsinki

The Investigator will ensure this study is conducted in full compliance with the principals of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever, affords the greater protection to the subject. The study must fully adhere to the principles outlined in 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 consent form should be translated and communicated to the subject in a language that is understandable to the subject. Certified translations of the informed consent documentation will be provided as applicable.

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

Tests performed as standard of care prior to documentation of consent may be used for screening results as appropriate (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 (CSR) according to ICH guideline E3: Structure and Content of Clinical Study Reports.

10.1.10. Publication Policy

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

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

10.1.11. Financial Disclosure

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

10.2. Appendix 2: Safety Reviews

10.2.1. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be implemented for this study for Cohort 1 only 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 after approximately 5, 15, and 30 subjects have been dosed. At the time of Protocol Amendment 3, the DSMB has held 2 operational meetings to review data from after dosing of 5, and 15 subjects. Both meetings resulted in the DSMB recommendation to continue the study without protocol modification. The final DSMB meeting will be held after the 30th subject has been dosed in Cohort 1.

A DSMB charter, defining roles and accountabilities and the process for review, is available.

10.3. Appendix 3: Clinical Laboratory Tests

Table 4: Protocol-Required Safety Laboratory Assessments

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

Hematology:	Red blood cell count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Mean cell volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Reticulocytes (absolute) Platelet count White blood cell count (WBC) 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 Creatinine Chloride Glucose BUN or Urea
Other Tests:	Ferritin C-reactive protein

Coagulation Screen:	Prothrombin time (PT) *or* International Normalized Ratio(INR) Activated partial tissue thromboplastin time (aPTT)
Pregnancy Test:	Serum beta-HCG or Urine test
Thyroid Function 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[#] EBV (EBNA)[#] Treponema IgG or RPR [#] **Viral reactivation** CMV DNA PCR – peripheral blood for detection of reactivation. In the event of suspected end organ CMV disease a biopsy may be required [#] Per Institutional Standard Practice is acceptable

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) ≥ CTCAE grade 3 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 fulfil the definition of an AE or SAE.

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

10.4.2. 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).

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

g. Additional protocol-defined criteria

- Any Grade ≥3 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 (see Section 10.4.5):
  - ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)
  - ALT ≥3xULN 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 CRF.

- 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 CRF 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 will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. See Section 10.5.6 and Section 10.4.7 for guidance on grading of CRS and ES respectively. For Aes not specifically listed in the CTCAE, The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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.

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.

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.

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 CRF.
- 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 SAE worksheet (SAEW) within 24 hours of the study personnel's discovery of the event.
• Complete the SAEW as fully as possible and obtain the Investigators signature. Create a PDF of the signed SAEW and submit to:
  • [redacted]
  • [redacted]
• Do not delay reporting an SAE if the Investigator is unavailable to sign. Report the SAE as above and provide a copy of the signed SAEW as soon as possible afterwards.

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 Time and Events Table (Section 1.3), and as clinically indicated.

If a Subject meets one of the criteria defined in Table 5, 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 (see Section 1.3). Hepatic safety assessments will be included in this safety follow up.

Table 5: Hepatic Monitoring Criteria

Hepatic Monitoring Criteria	
ALT Absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[1]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[2]	ALT ≥3xULN 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 electronic case report form (eCRF), and a serious adverse event worksheet	• Viral hepatitis serology[3]

(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, 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 ≥2xULN	• Serum CPK and LDH • CBC with differential to assess eosinophilia • PBMC blood sample for persistence[4] • Assess for the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) and alcohol use • **For bilirubin or INR criteria:** • Hepatologist consultation required • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) • Consider liver biopsy

1. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.
2. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
3. Includes:Hepatitis A immunoglobulin M (IgM) antibody; HbsAg and HbcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
4. Record the date/time of the PBMC blood sample draw on the CRF. 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, 2006; FDA, 2010; EMA, 2009]. Subjects will be followed according to the schedule outlined in

Section 1.3.2 , 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 to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled, and submitted within the annual report of the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment.

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, cytokine release syndrome, 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 is recommended in all subjects. G-CSF (i.e., filgrastim) should be used for management of neutropenia according to ASCO guidelines [Smith, 2015]. G-CSF should be given on Day -3 until resolution of neutropenia (reaching an ANC of at least 2×10^9/L to 3×10^9/L or as per institutional practice).

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

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-A2M4 cell infusion should be immediately referred to an infectious disease specialist for consideration of anti-viral therapies. Investigators should also consult the latest guidelines/instituitional policies pertaining to the management of COVID-19 in cancer/cell therapy patients. The Medical Monitor should be be informed if a subject has a positive COVID-19 test (irrespective of symptoms) after receiving either lymphodepleting chemotherapy or ADP-A2M4 cell infusion.

10.5.3.2. Pneumocystis carinii Pneumonia

Subjects should receive prophylaxis against Pneumocystis pneumonia with drug, dose and duration according to institutional guidelines. Single strength trimethoprim sulfamethoxazole daily is the recommended first line agent, starting at day 28 for one year. Other regimens including atovaquone (1500 mg daily with food) or aerosolized pentamidine (300 mg every four weeks) are also acceptable, e.g. sulfonamide allergy, and 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 HSV episodes.

10.5.3.4. Cytomegalovirus

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. If CMV viremia is detected at baseline, treatment should be initiated and evidence of viral clearance obtained, prior to lymphodepletion chemotherapy. All CMV seropositive subjects will continue to be monitored for CMV viremia by CMV DNA PCR as shown in Table 1 until 60 days post infusion of ADP-A2M4. 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 (300mg daily), entecavir (0.5mg daily), or tenofovir (300mg 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 antifungal 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 x10^9/L, Hb > 8.0 g/dL (or in accordance with institutional practice) and as clinically indicated. See AABB Guideline on platelet transfusion [Kaufman, 2015].

10.5.4.1. 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 allogeneic 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.

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 PI should be contacted and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the ADP-A2M4 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

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 many of which mimic infection including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash and dyspnea. It is important to evaluate the subject for concurrent infections. Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure and disseminated intravascular coagulation. CRS may also be associated with findings of macrophage activation syndrome or occur coincident with tumor lysis syndrome.

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

Table 6 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical, and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels (Section 8.6.2) ferritin (Section 8.4.21), as well C-reactive protein (CRP) (Section 8.4.20) levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 6: Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment	Management Guidelines
1	Constitutional symptoms not life-threatening (e.g., fever, nausea, fatigue, headache, myalgias, malaise)	• Vigilant supportive care[1] • Assess and treat for possible infection[2] • Consider anti-IL-6 therapy[3] (tocilizumab 8 mg/kg* IV) if clinically indicated (i.e., subjects with symptoms persisting ≥ 24 hours or subjects with co-morbidities or subjects of older age)
2	Symptoms require and respond to moderate intervention (Hypotension responds to fluids or one low dose pressor, hypoxia responds to <40% O_2, and/or Grade 2 organ toxicity)	• Monitor cardiac and other organ function • Vigilant supportive care[1] • Assess and treat for possible infection[2] • Treat hypotension with fluid and pressors. • Administer O_2 for hypoxia. Administer anti-IL-6 therapy[3] (tocilizumab 8 mg/kg* IV) at any time if clinically indicated (i.e., subjects with symptoms persisting ≥ 24 hours, or subjects with co-morbidities or subjects of older age)

3	Symptoms require and respond to aggressive intervention hypotension requires multiple pressors or high dose pressors hypoxia requires ≥40% O^2, Grade 3 organ toxicity or Grade 4 transaminitis	• Monitor subject very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). • Vigilant supportive care[1] • Assess and treat for possible infection[2] • Treat hypotension with fluid and pressors. Administer O_2 for hypoxia. • Administer anti-IL-6 therapy[3]
4	Life-threatening symptoms Grade 4 organ toxicity (excluding transaminitis)	• Manage subject in ICU • Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required • Administer anti-IL-6 therapy[3]
5	Death	

1. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure
2. Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of antimicrobial agents for concurrent bacterial infections, and for treatment of fever and neutropenia as per institutional practice; and antipyretics, analgesics as needed.
3. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first line treatment (tocilizumab 8 mg/kg* IV).

   *The maximum dose for tocilizumab is 800 mg per dose. Corticosteroids can be used for subjects refractory to anti IL-6 therapy. Other immunosuppressor agents may also be used, including TNFα and IL-1R inhibitors. Please see text below for details.

Source: Lee, 2019; Neelapu, 2018

For subjects requiring immunosuppressive intervention anti-IL-6 therapy should be the first line treatment. Tocilizumab is a humanized anti-IL-6 receptor antibody that has been approved for the treatment of CRS. Anecdotally, tocilizumab has produced rapid and complete correction of

CRS with single doses [Maude, 2014]. The United States product insert (USPI) for tocilizumab recommends a dose of 8 mg/kg administered over 1 hour in adult subjects as the first-line treatment of severe CRS. Subjects may receive a repeat dose(s) if clinical signs and symptoms do not improve at least 8 hours apart. Refer to Section 10.5.7 below for subjects experiencing Immune Effector Cell-Associated Neurotoxicity Syndrome concurrent with CRS.

Second-line, tocilizumab refractory, management of CRS is at the discretion of the Investigator following local institutional policy. This can potentially include the use of corticosteroids either in combination with a second dose of Tocilizumab [Maus, 2020] or a corticosteroid administered as a single agent after two doses of Tocilizumab have been administered and if CRS symptoms are persisting. Use of steroid sparing agents (e.g. siltuximab or anakinra) is at the discretion of the Investigator.

Lee [2019] recommend steroids as second-line therapy for CRS as the response to anti-IL-6 therapy may be more rapid and owing to the potential of steroids to attenuate the anti-tumor effects of the adoptive T cell therapy. However, in subjects with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability (See Section 10.5.7) or other life-threatening symptomatology, consideration may be given to the use of corticosteroids as immunosuppressive therapy. High doses (e.g. 2 mg/kg/day prednisone equivalent) may be required.

If cytokine release syndrome is suspected, a physician with expertise in the management of subjects following bone marrow transplant should be consulted. If high dose corticosteroids are required, treatment should generally be continued until resolution to Grade 1 followed by tapering doses over several weeks.

Please refer to the most recent version of the product label for tocilizumab and the latest Society for Immunotherapy of Cancer (SITC) guidelines for CRS [e.g. Maus, 2020].

10.5.7. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

See Section 8.5.7.2 for a description of ICANS. Neelapu, et al [Lee, 2019] have developed a grading system for ICANS which incorporates the Immune Effector Cell-Associated Encephalopathy 10-point neurological assessment (ICE) tool, see Table 7. Points are assigned for each of the tasks in Table 7 which are performed correctly. Normal cognitive function is defined by an overall score of 10.

The ICE should be used to monitor all subjects for ICANS.

Table 7: ICE-point neurological assessment [based on Lee, 2019]

Task	ICE Points
Orientation: Orientation to year, month, city, and hospital,	Total of 4 points (one point for each)

Task	ICE Points
Naming: Ability to name three objects(e.g. point to: clock, pen, button)	Total of 3 points (one 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 score is used in grading of ICANS as presented in Table 8.

Table 8: Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score[1]	7–9	3–6	0–2	0 (patient is unarousable, and unable to perform ICE)
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizures	NA	NA	Any clinical seizure, focal or generalized that resolves rapidly or nonconvulsive seizures on 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]	NA	NA	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Elevated ICP/ cerebral edema	NA	NA	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

Source: Based on Lee, 2019

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
[1] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE 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.

10.5.7.1. Management of ICANS

The recommended management of ICANS should be based on toxicity grade. Table 9 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. For subjects with neurologic symptoms refractory to an initial dose of anti-IL-6 therapy, consider siltuximab for the second dose based on its mechanism of action directly against IL-6.

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

Table 9: Management of ICANS

Grade	Treatment
1	For all patients: • Vigilant supportive care; aspiration precautions; intravenous (IV) hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired • Avoid medications that cause central nervous system depression • Evaluate for other contributing causes and treat accordingly Unless symptoms are mild and transient (e.g. 1 point change in ICE for less than 12 hours): • Neurology consultation including funduscopic exam to assess for papilledema • MRI of the brain with and without contrast (CT scan of the brain if MRI is not feasible). Further testing if indicated such as diagnostic lumbar puncture with measurement of opening pressure if increased intracranial pressure is suspected, or MRI spine if the subject has focal peripheral neurological deficits • Institute levetiracetam therapy and consider EEG if seizure activity is suspected • Consider anti-IL-6 therapy with tocilizumab 8 mg/kg[1] IV or siltuximab 11 mg/kg IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent CRS
2	• Supportive care and neurological work-up as described for grade 1 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 patient 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 (CSF) opening pressure <20 mmHg should be treated with a corticosteroid regimen as per Grade 4 below. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 ICANS

Grade	Treatment
4	• Supportive care and neurological work-up as indicated for grade 1 ICANS • Consider neurosurgical consultation for patients with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 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 800mg

10.5.8. Management of Prolonged Cytopenia

10.5.8.1. Definition of prolonged cytopenia, pancytopenia and plastic 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 EU SmPC; KYMRIAH USPI; YESCARTA EU SmPC; YESCARTA UPSI]. 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 a rare hematological disorder and is defined as diagnosis of severe aplastic anemia made in the setting of a hypocellular bone marrow when 2 of the following 3 blood counts are met: Absolute Neutrophil Count < 500/µL, Absolute Reticulocyte Count < 60,000/µL, and Platelet count < 20,000/µL with the exclusion of myelodysplastic syndrome.

Subjects may be symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. 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.

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 and 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 (ATG), cyclosporine, eltrombopag) as well as antimicrobial prophylaxis/therapy with the advice of your Hematology/Infectious Diseases consultant(s). If high dose corticosteroids are initiated, duration of therapy and 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:

- Female subjects of childbearing potential (FCBP) must agree to use an 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.
- 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 continuing 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 long-term follow up.

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-A2M4.
- 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)

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

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

10.7.1.2. Insertional oncogenesis

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidance [FDA, 2006a; FDA, 2006b; EMA, 2009]. Insertional oncogenesis is a theoretical risk in T cells transduced with a lentiviral vector. T cells appear resistant to transformation by integrating viruses [Cattoglio, 2010; Newrzela, 2008]. However, there are cases of oncogenesis with γ-retroviral transduced stem cells. Four of nine subjects with X-linked severe combined immunodeficiency (SCID-X1) treated with retrovirus transduced stem cells were found to have insertion near the LMO2 proto-oncogene promoter, leading to aberrant transcription and expression of LMO2 which resulted in acute T-cell lymphoblastic leukemia [Hacien-Bey-Abina, 2003; Hacien-Bey-Abina, 2014]. Additionally, two subjects treated for X-linked chronic granulomatous disease (X-CGD) with retroviral transduced stem cells demonstrated insertional activation of the EVI1 transcription factor which resulted in genetic instability, monosomy 7 and clonal progression toward myelodysplasia [Stein, 2010].

10.7.2. Testing for RCL and Persistence

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. The scheme for RCL testing is presented in Figure 1 below. RCL testing and monitoring will take place on subject's peripheral blood mononuclear cells (PBMCs) which will be collected at Baseline and then at 3, 6, and 12 months post-infusion and annually from year 2-15. Samples will be tested for the presence of VSV-G DNA copies.

If all samples are negative in year one, PBMC samples will be collected and archived annually until 15 years 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. The DSMB will be notified and a review by Adaptimmune's Safety Review Team and Safety Governance Board will take place.

Response to potential outcomes of second test:

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

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

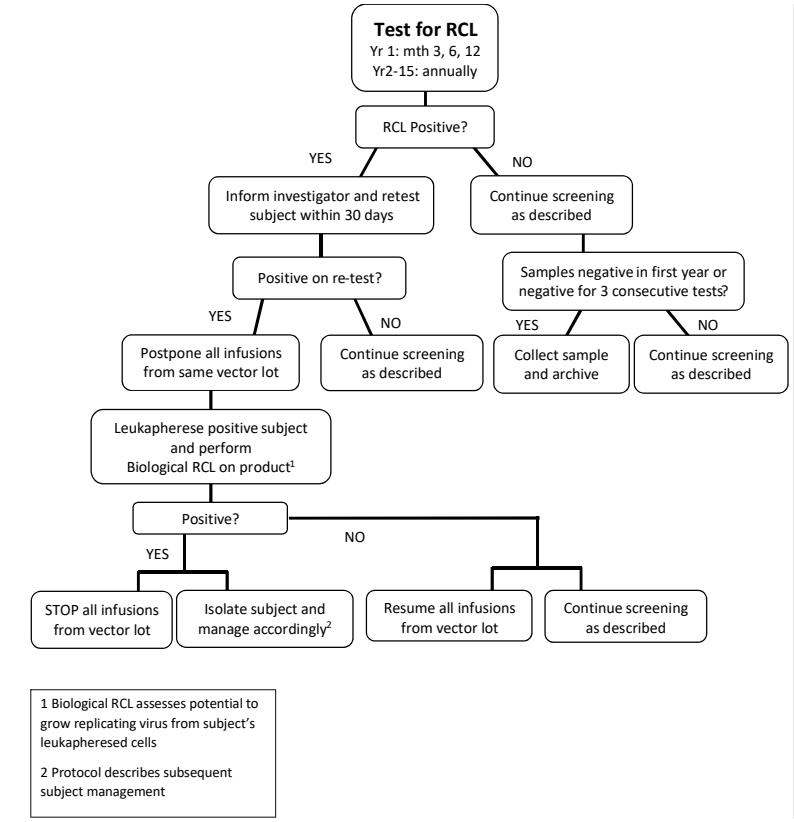
If the biological RCL test is negative, infusions for all subjects can resume.

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

The following approaches have been discussed for subject management:

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

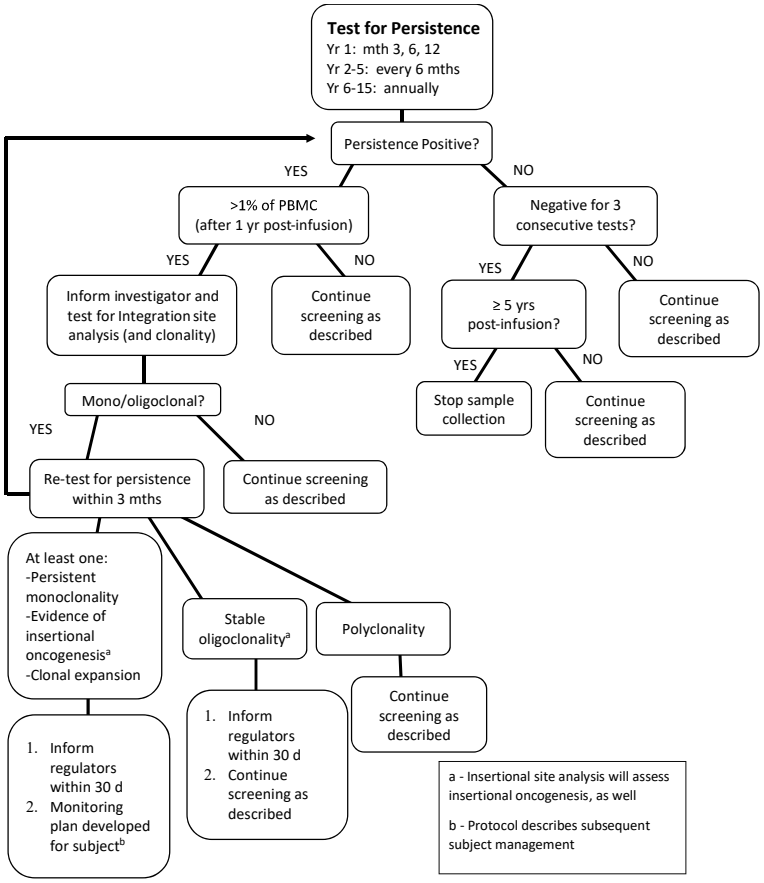
Figure 1: Flow chart for testing for Replication Competent Lentivirus (RCL)



PBMC samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects. Subject samples will be tested for persistence at 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, 2006a; FDA, 2006b; EMA, 2009]. The scheme for testing for persistence is presented in Figure 2.

The samples will be tested using a PCR-based method to detect the presence of the integrated vector sequences Psi DNA, both of which are part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion, greater than 1% PBMCs test positive for vector sequences, the subject's PBMCs will be evaluated for integration site analysis (see 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 insertional oncogenesis.

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

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

monitoring plan specific to the health care risk and strategies to inform appropriate subjects, investigators, FDA and other regulators of the findings.

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

10.7.4. Letter to Physician – LTFU notification

[date]

[name and address]

Dear [physician name],

Your patient [patient name] has participated in a clinical research study, [interventional study name and number], that requires 15 year monitoring for adverse events. To aid in reporting of adverse events that are possible related to the clinical research study, we are asking the patients on our research study to designate a primary care or infectious disease physician that may help in the monitoring and reporting of adverse events. Your patient has designated you. If upon any of your visits with your patient, any of the following events are reported or discovered, please contact the study nurse or physician as soon as possible:

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

If your patient experiences any of these events, please refer them back to their study physician. Please contact the study coordinator below as soon as you can so that they can record the event and then monitor your patient's health if necessary. When you call, remember to mention the protocol number of the study which is ADP-0044-002, patient ID [XXX] and the study title which is "A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma"

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 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 with contrast is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Ultrasound (US) should not be used to measure tumor lesions. The same modality should be used when comparing or making assessments.

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

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

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

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

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

Measurable lesions

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

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

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

Non-target Lesions

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

Evaluation of Target Lesions

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

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

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

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

Special notes on the assessment of target lesions:

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
- Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.
- Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

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

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

Non-CR/Non-PD:

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Special notes on assessing progression of Non-Target lesions

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

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

New lesions

The appearance of new malignant lesions denotes disease progression:

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

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

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

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

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

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required**[1]
CR	CR	No	CR	≥4 wks. Confirmation[2]
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation[3]
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. from ADP-A2M4 infusion
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 for further details on what is evidence of a new lesion [Eisenhauer, 2009]
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. Confirmation of response is established by no evidence of disease progression at the subsequent time point. 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 Non-evaluable Designation

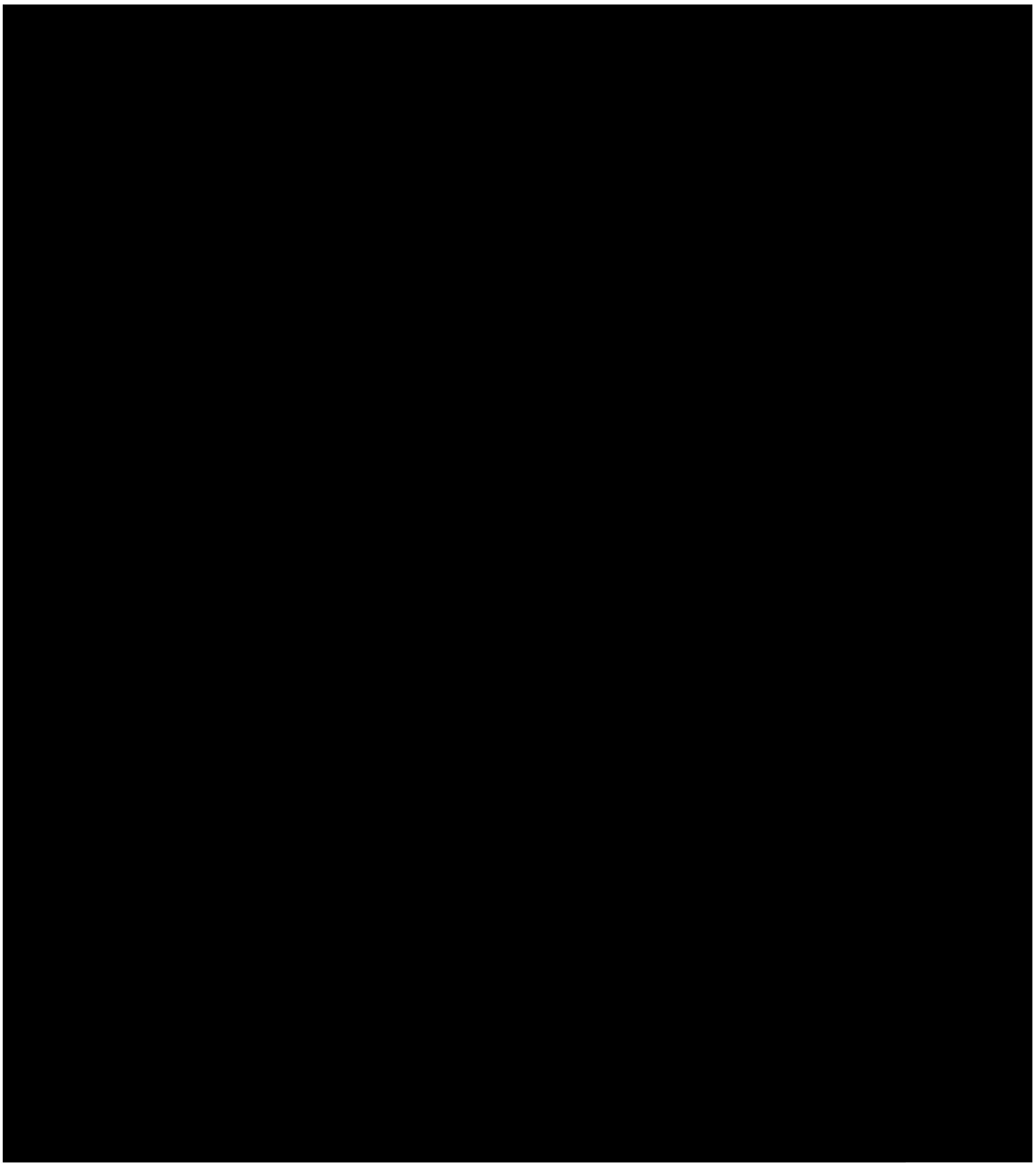
When no imaging/measurement is done at all at a particular time point or the imaging is technically unreadable, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a 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.

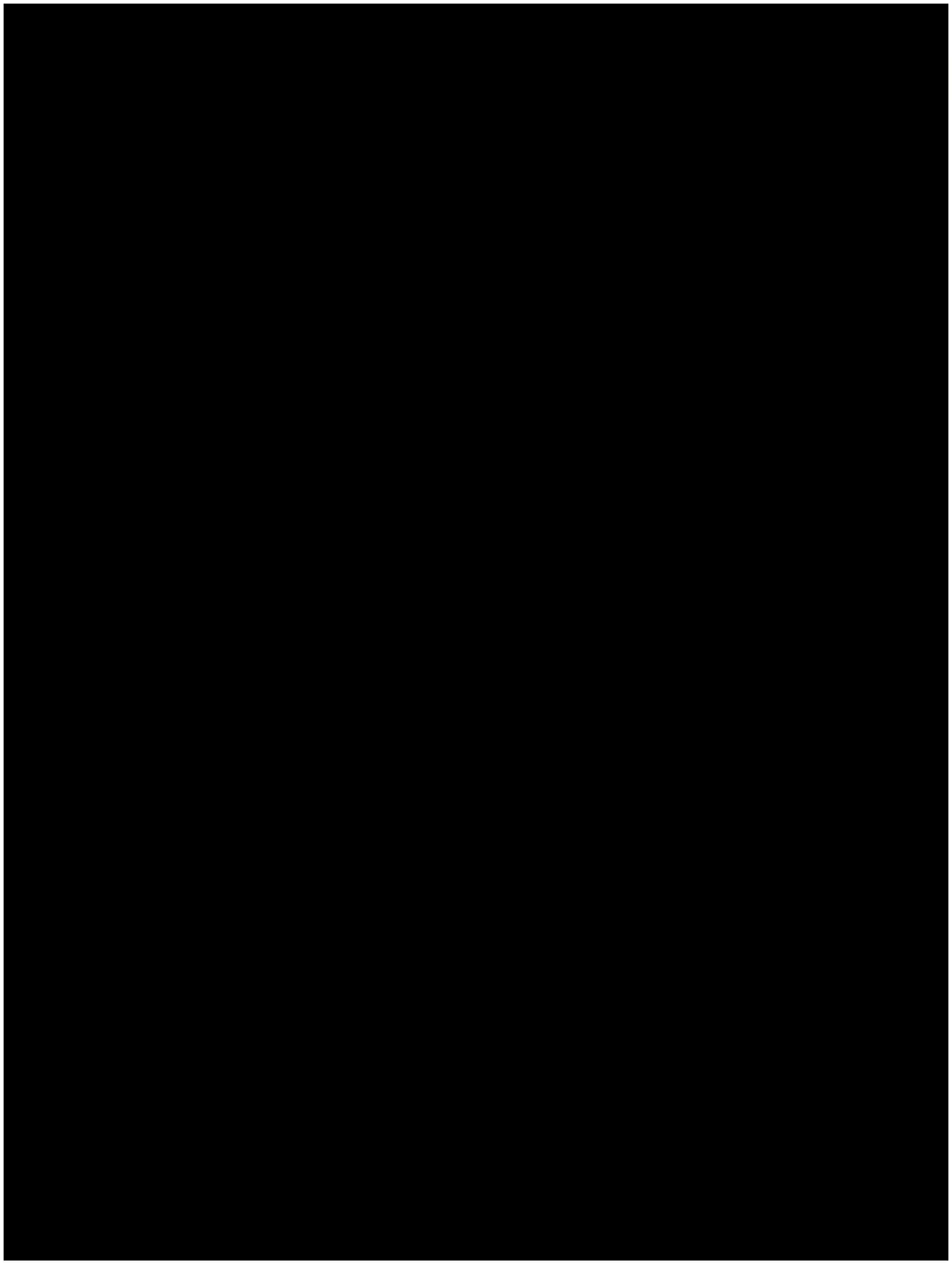
10.9. Appendix 9: ECOG Performance Status

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

[Oken, 1982]

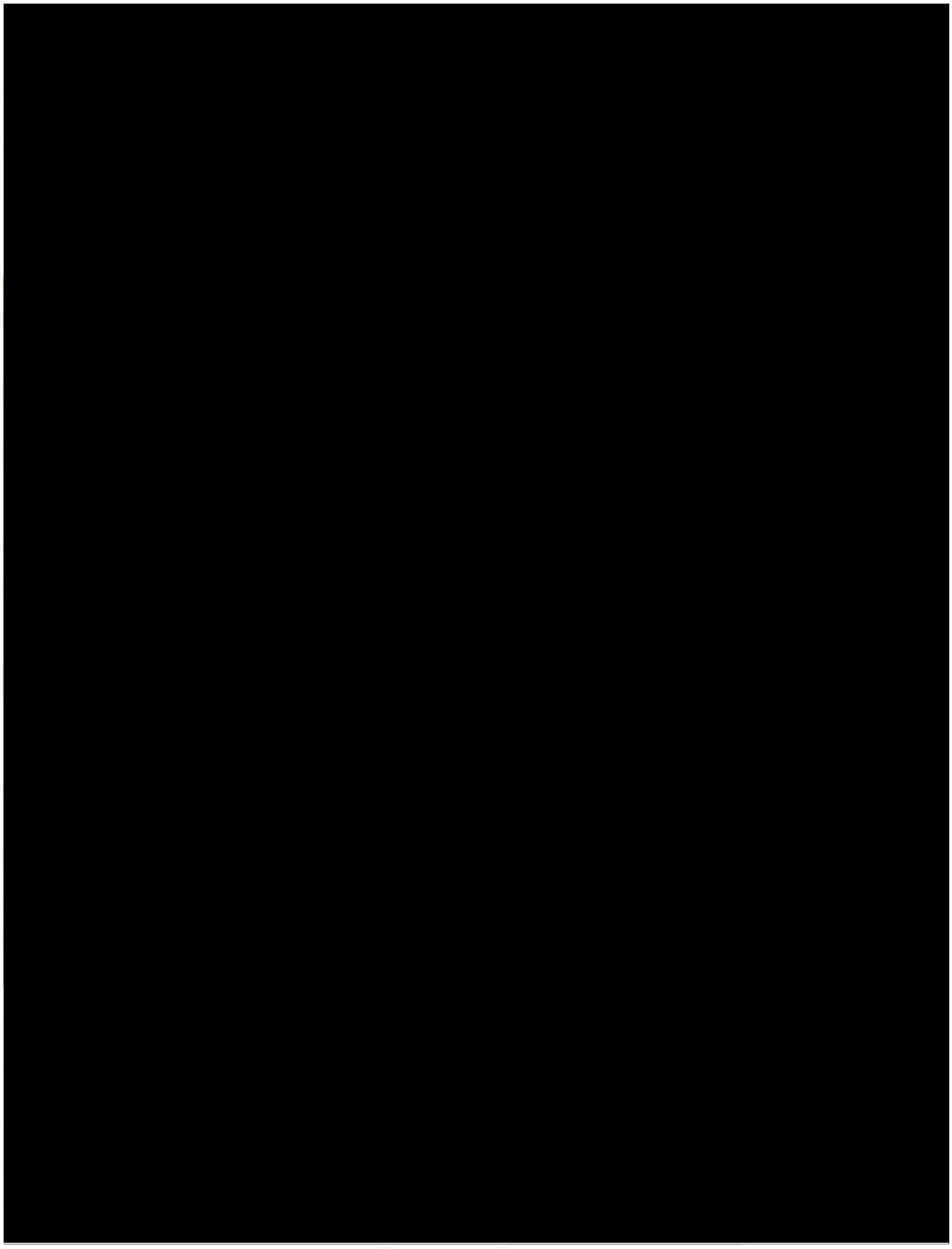
10.10. Appendix 10: EQ-5D-3L Health Questionnaire (SAMPLE)





10.11. Appendix 11: [redacted]

ENGLISH



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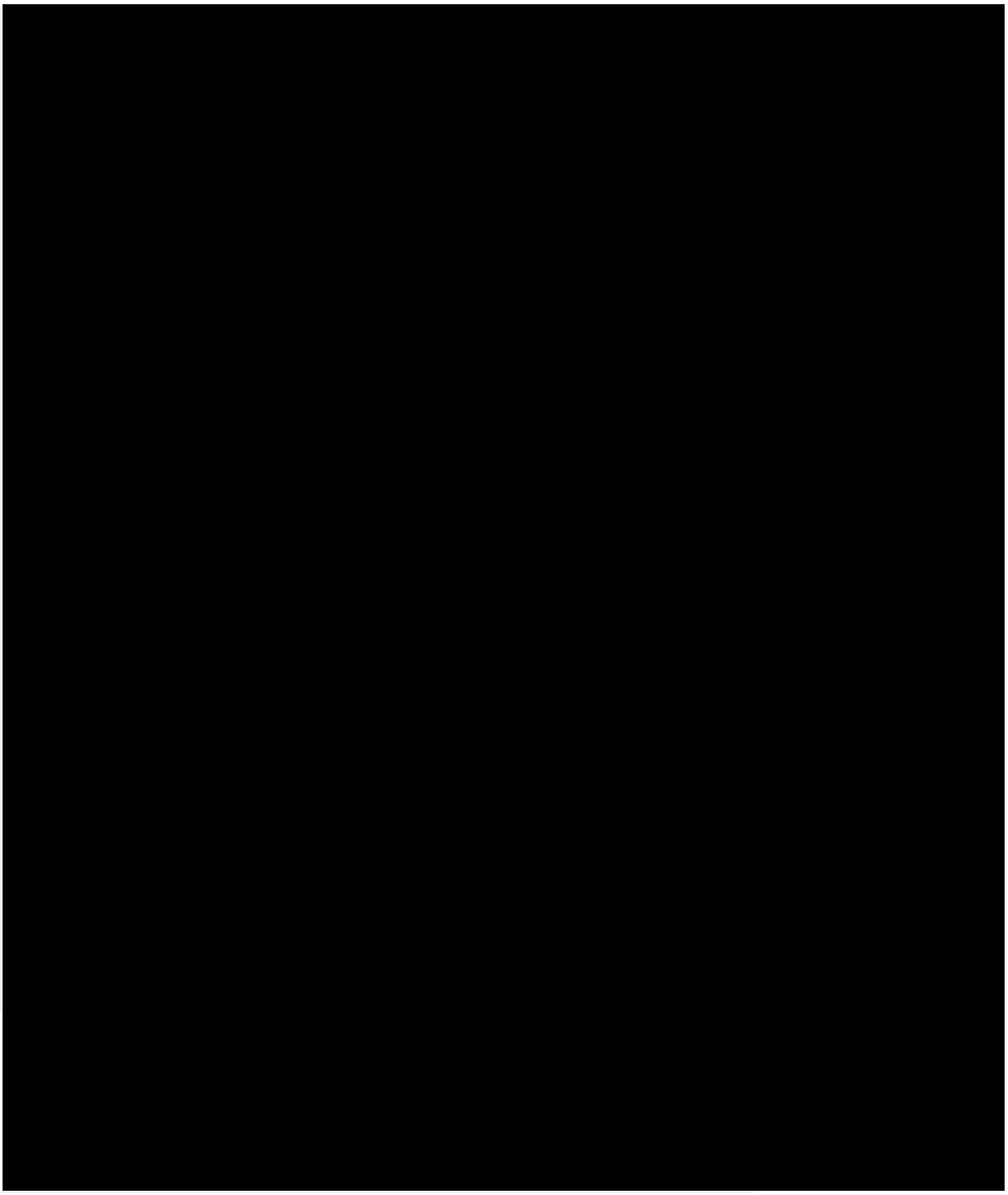

10.12. Appendix 12: Abbreviations

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

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

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

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

NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal Investigator
PTT	Partial thromboplastin time
PR	Partial response
qPCR	Quantitative polymerase chain reaction
RAC	Recombinant DNA Advisory Committee
RC	Research Committee
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
SCID-X	Severe combined immunodeficiency disease – X linked
SD	Stable disease
SGPT	Serum glutamate-pyruvate transaminase
SIN	Self-inactivating
SOP	Standard operating procedure
SPEAR	Specific Peptide Enhanced Affinity Receptor
SPM	Study Procedures Manual
SUSAR	Suspected, unexpected serious adverse reactions
TCR	T cell receptors
TILs	Tumor-infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor

TTR	Time to response
TURBT	Transurethral resection of bladder tumor
ULN	Upper limit of normal
VSV-G	Vesicular Stomatitis Virus G glycoprotein
WBC	White blood cell
WHO	World Health Organization
X-CGD	X-linked chronic granulomatous disease

10.13. Appendix 13: Protocol Amendment History

Protocol Amendment 2 dated 20March 2020 is replaced by Protocol Amendment 3 dated 05February 2021.

Sections amended	Change	Rationale for change
1.3.1, 4.1.1, 4.2.1.1,	Inclusion of additional requirements for remote • consenting for buccal swab (HLA) and /or MAGE-A4 antigen testing. • Testing for HLA with buccal swab	Updated to provided clarification of requirements when remote screening is performed
1.3.1, 6.2.1, 8.4.10	Inclusion of adjustment of fludarabine dose for subjects with renal impairment	Updated to give additional clarification
1.3.1, 3, 8.7.2, 9.3.3, 10.11	Inclusion of EORTC-QLQ-C30 questionnaire for subjects participating in Cohort 2	New questionnaire is to be used In subjects in cohort 2
1.1, 1.3.1, 8.3.1	Clarification that CT/MRI scans conducted between Week 4 to Week 16 should be at least 28 days apart	Conducting scans 28 days apart ensures compliance with RECIST 1.1 requirements
2.2.3	Updated data pertaining to safety and efficacy of ADP-A2M4	Make consistent with current ADP-A2M4 Investigator's Brochure
1.1, 2.1, , 2.2.4, 4.1, 4.2, 5.1, 5.2, 8.2.3	Inclusion of Cohort 2 in synovial sarcoma subjects	Incldue Cohort 2 for synovial sarcoma patients subjectss
2.2.4, 2.2.5,	Amended to align with current available data	Aligned with current known data surrounding synovial sarcoma
3, 9, 9.1, 9.2, 9.3.2, 9.3.3	Inclusion of separate Cohorts 1 & 2	Additional cohort has been added to further assess

		patients with synovial sarcoma
1.1, 4.1, 4.2, 5.5, 9.2	Clarification that first 45 subjects will be included in Cohort 1 and addition of subsequent independent Cohort 2	Language added to clarify how many subjects will be dosed in each cohort
1.1, 3, 9.3.2, 9.3.3	Clarification that the primary efficacy endpoint is Overall Response Rate per RECIST v1.1 by independent review for Cohort 1. Secondary endpoints and safety endpoints were updated to reflect addition of new cohort.	Language updated to reflect addition of new cohort and that no new hypotheses testing is required.
4.3	Additional evidence for dose included	Provide evidance for dose range up to 10×10^9
1.1, 5.2	Inclusion criteria expanded for subjects who have previously received anthracycline or ifosfamide	To provide clarification of systemic therapy inclusion
1.1, 5.2	Inclusion laboratory values table updated	Clarification of inclusion criteria based on ANC, Prothrombin Time or INR, and GFR
1.1, 5.3	Updated exclusion criteria for subjects who have a history of Symptomatic CNS metastases	Updated to clarify and be clearer regarding exclusion of patients with a history of Symptomatic CNS metastases
1.1, 5.3	Exclusion of subjects with incipient compression/occlusion of a vital structure	Included in exclusion criteria following safety event and as recommended by FDA
1.1, 5.3, 10.5.3.1	Addition of COVID-19 requirements	Information added for COVID-19 requirements
6.1	Updated to allow for local luekapheresis	Updated to allow local leukapheresis

6.2	Granulocyte colony stimulating factor (G-CSF) guidance updated	Updated to align with current safety data
6.5.2, 6.5.2.1	Addition of Guidance on COVID-19 vaccinations	Updated to clarify guidance related to COVID-19 vaccinations
8.1.2	Updated to reflect additional information on disease history to be collected in eCRF	Updated to include site and size of tumor as well as last known tumor stage
8.4.8.1	Updated to confirm that QTcB or QTcF are acceptable	Updated to confirm that QTcB or QTcF are also acceptable for collection
8.4.13	Updated to clarify requirements for administration of anticoagulants.	Updated to clarify the need for either a low molecular weight heparin injection or a novel oral anticoagulan
8.6.3	Clarification of timing of Baseline liquid biopsy collection	Updated to include collection at baseline
9.1	Reference to CDx analysis population removed	Removed as information regarding CDx analysis is held outside of protocol
9.1	Reference to PP Polulation removed	Based on subjects enrolled to date no major protocol violations where subjects will be excluded from primary analysis
9.3.3	Removed reference to QOL exploratory endpoints.	Analysis of exploratory endpoints will be addressed in the Statistical Analysis Plan
10.4.1	Events meeting the AE definition updated	Updated to give clarity
10.4.4	SAE reporting updatedto remove location of SAEW	Nore required to be referenced in protocol

10.5.4.1	Irradiated Blood Product section updated	Updated as per latest guidance
10.5.6	Updated Management of CRS	Updated as per latest guidance
10.5.8	Updated Management of prolonged cytopenia	Updated as per latest guidance
5.2, 8.4.9, 9.3.2, 10.2.1, 10.3, 10.4.6, 10.4.7	Administrative	Administrative updates, corrections and clarifications

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Study Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

NCT number: NCT04044768

Document: Protocol

Document Date: 02 Mar 2021

PROTOCOL NUMBER ADP-0044-002

A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

(SPEARHEAD 1 STUDY)

PROTOCOL VERSION: AMENDMENT 3, UK VERSION 3.0

DATE: 02MAR2021

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T Cells in Subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma (MRCLS)

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-A2M4 Investigator's Brochure.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T Cells in Subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma (MRCLS)

Product Name: ADP-A2M4

Protocol Number: ADP-0044-002

IND Number: 17235

EudraCT Number: 2019-000589-39

DATE OF ORIGINAL PROTOCOL: 25FEB2019

Amendment Number	Date	Reason for Change
Original	25FEB2019	NA -
Amendment 1	04JUN2019	Change in the lymphodepletion regimen Addition of ECG at Day 5 Added upper age limit Increase entry criteria for ANC, platelets, GFR Additional exclusion criteria under uncontrolled intercurrent illness Emerging data for ADP-A2M4 added Updated study physician Administrative changes

Amendment Number	Date	Reason for Change
Amendment 1, UK Original (UK-1.0)	02DEC2019	MHRA requested changes: - requirement for 10 days hospitalization - clarification of subject access to intensive care unit - updated contraceptive guidance - requirement for serum pregnancy test at screening - clarification of clinically significant Grade 1 or 2 lab abnormalities reported as AE - added guidance for diagnosis and management of GVHD - added 2 additional stopping criteria - added ECG Day 2 - added exclusion for history of brain metastasis Administrative changes

Amendment Number	Date	Reason for Change
Amendment 2	08JUN2020	Updates and clarifications to HLA criteria Removed futility analysis and associated protocol aspects Updated number of subjects Decreased duration of enrollment Increased LVEF criteria Clarification of washout for prior gene therapy Added updated data from current ADP-A2M4 Investigator's Brochure Update to CRS management guidelines Updated Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells Inclusion of optional remote consent for MAGE-A4 tissue testing and/ or buccal/ mouth swab test for HLA assessment at participating sites Administrative changes and clarifications

Amendment Number	Date	Reason for Change
Amendment 3, UK Original (UK-3.0)	02MAR2021	Update to sponsor contacts Addition of Cohort 2 (45 synovial sarcoma subjects) Updates to safety and efficacy information to align with current IB Information added for COVID-19 requirements Exclusion for compression/occlusion of a vital structure added Addition of EORTC QLQ-C30 (Cohort 2 only) Removal of CDx and PP Population definitions Additional details added throughout for additional clarity of wording Template language updated

CONFIDENTIALITY STATEMENT

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

[redacted]

[redacted]

[redacted]

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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1. PROTOCOL SUMMARY

1.1. Synopsis

Title A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma	
Short Title	SPEARHEAD 1 Study
Protocol Number	ADP-0044-002
Phase	2
Methodology	Subjects with advanced synovial sarcoma or myxoid/myxoid round cell liposarcoma (Cohort 1 only) will be Pre-screened to determine appropriate human leukocyte antigen (HLA) and tumor antigen status. Only subjects with advanced synovial sarcoma will be eligible for Cohort 2. Only subjects expressing at least 1 HLA-A*02 inclusion allele and no exclusion allele and whose tumor expresses the MAGE-A4 antigen above the 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 into either Cohort 1 or Cohort 2. Enrolled subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the ADP-A2M4 cell Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation. Subjects who have enrolled into a Cohort may not enroll into the other Cohort subsequently. Prior to the administration of lymphodepleting chemotherapy all eligibility criteria will be reconfirmed and baseline tumor assessment obtained. Anticancer therapy may be administered between screening and leukapheresis and between leukapheresis and the start of lymphodepletion (bridging therapy), if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods must be adhered to. When the ADP-A2M4 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days

	-7 to -5) followed by infusion of ADP-A2M4 cells on Day 1. Subjects will remain hospitalized for observation for at least 10 days post T cell infusion. An independent Data Safety Monitoring Board (DSMB) will review the ongoing safety during the interventional phase of the study for Cohort 1. Cohort 2 will begin once all subjects have been dosed in Cohort 1. Subjects in both cohorts will have the following study visits for assessment of eligibility, efficacy, safety, health related-outcome and biomarkers: Pre-Screening, Screening, Leukapheresis, Baseline, Lymphodepleting Chemotherapy (Day -7 to Day -4), T cell infusion (Day 1) and immediate post infusion monitoring (Day 1 through Day 8), weekly visits until Week 4 post infusion, then 6, 8, 12, 16 and 24 weeks then every 2 months until disease progression. Subjects will undergo disease monitoring by magnetic resonance imaging (MRI) or computerized tomography (CT) scan at Screening, Baseline, Week 4, Week 8, Week 12, Week 16 and Week 24, and every 2 months 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 6-15. The timepoint at which the subject switches will be driven by the timepoint at which the subject progresses e.g. 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 Primary Efficacy Analysis will be for Cohort 1 only. Clinical cut-off for the primary analysis will occur once the forty-fifth subject dosed in Cohort 1 has up to 6 months follow-up post T cell infusion. At this time, all safety and secondary efficacy endpoints for Cohort 1 only will also be summarized to provide supportive evidence to the primary assessment.
Study Duration	Enrollment is expected to continue for approximately 12 months for Cohort 1 and for an additional 12 months for Cohort 2. The study will be considered complete once all enrolled subjects complete 15 years of follow-up or discontinue the study for any reason.
Study Center(s)	The study will be conducted in approximately 24 sites in North America and Europe. Additional sites may be added at the discretion of the Sponsor.

Number of subjects	Ninety (90) subjects: Forty-five (45) synovial sarcoma and MRCLS subjects in Cohort 1; Forty-five (45) synovial sarcoma subjects in Cohort 2.

Objectives	**Endpoints**
Primary	
To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	Overall Response Rate (ORR) per RECIST v1.1 by independent review in Cohort 1.
Secondary	
To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	For Cohort 1 and across Cohorts (overall): • 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-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review across Cohorts (overall) For Cohort 1 and across Cohorts (overall): • Time to Response (TTR) • Duration of Response (DoR) • Best Overall Response (BOR) • Progression Free Survival (PFS) • Overall Survival (OS)
Development and validation of an in vitro diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Across Cohorts: • Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay

Characterize the in vivo cellular pharmacokinetics (PK) profile of ADP-A2M4 cells	For Cohort 1 and across Cohorts (overall): • Peak persistence and other relevant PK parameters of ADP-A2M4 cells
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Inclusion Criteria	1. Subject (or legally authorized representative) voluntarily agrees to participate by giving written Informed Consent (and Assent as applicable) in accordance with ICH GCP guidelines and applicable local regulations. 2. Subject (or legally authorized representative) agrees to abide by all protocol required procedures including study related assessments and management by the treating institution for the duration of the study, including long term follow-up. 3. Age ≥16 and ≤75 years at the time the Pre-screening informed consent/assent is signed.

	4. Diagnosis of advanced (metastatic or inoperable) synovial sarcoma or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by cytogenetics. Inoperable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise. a. For Synovial Sarcoma (Cohort 1 and Cohort 2): confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)). b. For MRCLS (Cohort 1 only): confirmation by the presence of the reciprocal chromosomal translocation t(12;16) (q13;p11) or t(12; 22) (q13;q12) 5. Must have previously received either an anthracycline or ifosfamide containing regimen. 1st-line metastatic treatment with ADP-A2M4 is permissible if ifosamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumour setting. (Subjects who are intolerant of both anthracycline and ifosfamide must have previously received at least one other type of systemic therapy). 6. Measurable disease according to RECIST v1.1. 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. 8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥2+ staining in ≥30% of the cells by immunohistochemistry. 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%. 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 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 sexually active subjects are required to use a condom in addition to the female partner use of a highly effective form of contraception or must agree to abstain from heterosexual activity with a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide). 13. Must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support) within 7 days prior to lymphodepletion and leukapheresis
Platelets	≥ 100 x10^9/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Coagulation	
Prothrombin Time (PT) or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation
Renal	
Glomerular filtration rate (calculated CrCl using only the Cockcroft-Gault equation, or measured using either a 24-hr	≥ 60 mL/min

	urine creatine collection or a radionuclide EDTA test)[a]
	Hepatic
	Serum total bilirubin — ≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)
	Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT) — ≤ 2.5x ULN
	a) 24-hour urine creatine clearance or radionuclide EDTA tests should be used to measure the GFR in all subjects: ≥ 65 years old; clinically obese (≥ 30KG/m2) or underweight (≤18.5KG/m2); borderline low calculated CrCl (Cockcroft-Gault) at approximately 60mls/min. Renal function will be reassessed at Baseline using the same methodology.
Exclusion Criteria	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 (TKI) (e.g. pazopanib)	1 week	1 week
Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors,)	4 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	Subjects who have received a gene therapy using any DNA-integrating vector other than a lentivirus (retrovirus, AAV, etc.) are excluded from this study. Subjects who have received a gene therapy using a lentiviral vector may be eligible if they have persistence results below the lower limit of quantification (LLOQ) for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.	Not permitted after leukapheresis and prior to lymphodepletion.
	Corticosteroids or any other immunosuppressive therapy. NOTE: Use of topical steroids is not an	2 weeks	2 weeks

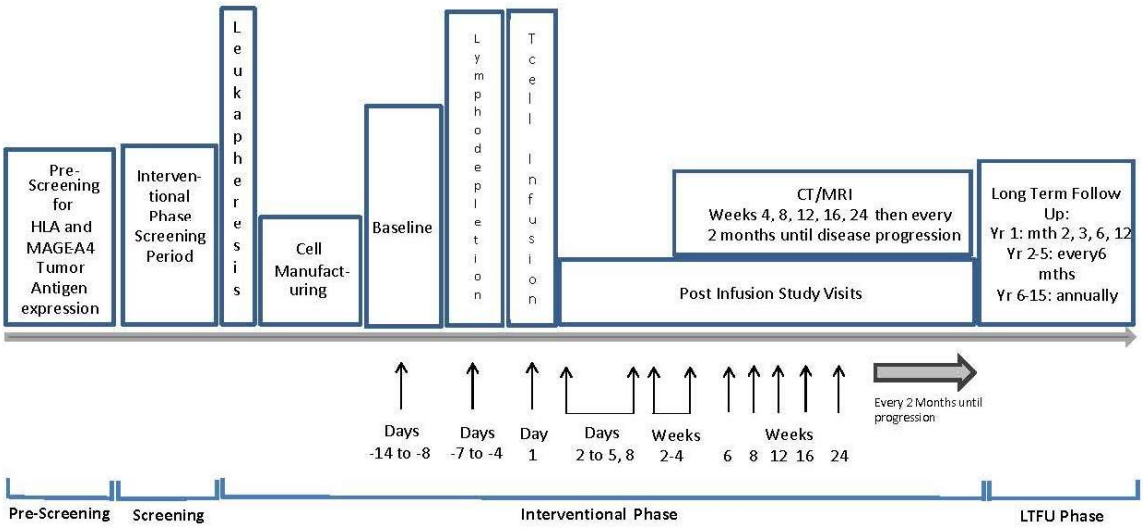
	exclusion. See Section 6.5.1 for exceptions.		
	Investigational treatment or interventional clinical trial	4 weeks	4 weeks
	Allogeneic hematopoietic stem cell transplant	Not permitted within any amount of time	Not permitted within any amount of time
	Radiotherapy to the target lesions	N/A	3 months. A lesion with unequivocal progression may be considered a target lesion regardless of time from last radiotherapy dose. (Note: there is no washout period for palliative radiation to non-target organs).
	Major surgery	N/A	4 weeks. Subjects must have recovered from any surgical 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, 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 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; • Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4; • Uncontrolled clinically significant arrhythmia; • Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months; • Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent); • Congenital or family history of long QT syndrome; • Current uncontrolled hypertension despite optimal medical therapy; • History of stroke or central nervous system bleeding; transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) in last 6 months; • Incipient compression/occlusion of a vital structure (e.g. bronchus; superior vena cava; renal outflow tract) which cannot undergo prophylactic stenting;

	• COVID-19 infection or a positive COVID-19 RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy. If a subject has a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart. 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 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.
Investigational Product, Dose, Route, Regimen	ADP-A2M4 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 primary clinical endpoint for efficacy is Overall Response Rate (ORR) defined as the proportion of subjects with a complete response (CR) or partial response (PR) via independently reviewed RECIST v1.1 relative to the total number of subjects in the analysis population in Cohort 1. The primary analysis population for safety and efficacy will be the modified intent to treat population (mITT) defined as all subjects who received the ADP-A2M4 cell infusion in Cohort 1.

	(Null Hypothesis) H_0: $p \leq p_0$, vs. (Alternate Hypothesis) H_1: $p > p_0$, where p_0 (historical control rate) = 0.18. Statistical assumptions include: • The type I error (α) will be no more than 0.025 • The type II error (β) will not exceed 0.1 • Exact Binomial methods will be used to test the hypothesis • The assumed ORR for ADP-A2M4 is 0.40. Based on the statistical design assumptions above and the hypotheses and clinical assumptions detailed in Section 9, the estimated sample size for the trial is 45 subjects in Cohort 1 for the primary analysis. An additional 45 subjects are to be enrolled in Cohort 2, although no formal hypothesis testing is planned for Cohort 2 or overall (across cohorts). The primary endpoint, ORR per RECIST v1.1 by independent review for Cohort 1, will be evaluated using a one-sided exact-based Clopper-Pearson 97.5% confidence interval (CI). If the lower bound of the 97.5% CI exceeds 18%, the trial has met the pre-specified threshold for demonstrating efficacy. The key secondary efficacy endpoints ORR per RECIST v1.1 by independent review across Cohorts (overall), TTR, DoR, 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. Two-sided 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, PK profile, 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. Efficacy and safety summaries will be displayed across tumor types (overall) and by tumor type. Efficacy and safety summaries will be displayed across cohorts (overall) and by cohort as indicated above. 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
Cell Manufact-uring
Baseline
Lymphodepletion
T cell Infusion
CT/MRI
Weeks 4, 8, 12, 16, 24 then every 2 months until disease progression
Post Infusion Study Visits
Long Term Follow Up:
Yr 1: mth 2, 3, 6, 12
Yr 2-5: every6 mths
Yr 6-15: annually
Days -14 to -8
Days -7 to -4
Day 1
Days 2 to 5, 8
Weeks 2-4
Weeks 6 8 12 16 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

Table 1: T&E for Pre-Screening and Interventional Phase

Written Informed Consent must be obtained prior to performing any protocol procedures. A Pre-screening 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.

			Interventional Phase																							
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7					±28	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																									Section 8.1.1
Inclusion/Exclusion	X	X		X																						Section 5
Disease History	X	X																								Section 8.1.2
HLA typing	X[12]																									Section 8.2.1

			Interventional Phase																						
	Pre-Screening	Screening[1]	Leukapheresis	Baseline	Lymphodepleting Chemotherapy				T-cell Infusion	Post-infusion Assessments													Every 2 Months	Study Discontinuation	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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
MAGE-A4 Expression	X																								Section 8.2.2
Cytogenetics testing for translocations		X[1]																							Section 8.2.3
Safety and Efficacy Assessments																									
Medical History		X																							Section 8.4.1
Physical Exam		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	Section 8.4.4
ECOG		X		X										X	X	X	X	X	X	X	X	X	X	X	Section 8.4.5

			Interventional Phase																						
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Height				X																					Section 8.4.7
Weight		X		X													X		X	X	X	X		X	Section 8.4.7
Vital Signs		X		X					X[2]	X	X	X	X	X	X									X	Section 8.4.6
ECG		X		X					X[3]	X			X												Section 8.4.8.1
Echo/MUGA		X																							Section 8.4.8.2
CT / MRI		X		X													X[14]		X[14]	X[14]	X[14]	X[14]	X	X	Section 8.3.1
Brain MRI		X[4]		X[5]																					Section 8.4.9
ICE									X	X	X	X	X	X											Section 8.4.19
GFR (estimated or measured)		X		X																					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	Section 8.4.11

			Interventional Phase																						
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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 8.4.12
Coagulation		X		X																					Section 8.4.13
Pregnancy Test		X		X																					Section 8.4.16
Infectious Disease Screening		X																							Section 8.4.17
CMV PCR				X					X[5]						X[5]		X[5]	X[5]	X[5]						Section 8.4.18
Thyroid Function Tests				X																					Section 8.4.14
C-reactive Protein[6]				X					X			X		X	X		X								Section 8.4.20
Ferritin[6]				X					X			X		X	X		X								Section 8.4.21
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.5

	Interventional Phase																							
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**												**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Persistence (Vector Copies)	X[10]	X[10]		X						X		X		X	X		X		X	X		X	X		Section 8.4.22 LTFU Table 2
RCL (VSV-G DNA)				X																X		X	LTFU Table 2		Section 8.4.23 LTFU Table 2
Leukapheresis, Lymphodepleting Chemotherapy and Investigational Product Administration																									
Leukapheresis			X																						Section 6.1
Fludarabine[11]					X[11]	X[11]	X[11]	X[11]																	Section 6.2
Cyclophosphamide					X	X	X																		Section 6.2
ADP-A2M4 Infusion									X																Section 6.3
Biomarker Assessments																									
Tumor Biopsy				X													X[7]							X	Section 8.6.1

			Interventional Phase																					
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**												**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Cytokine and Soluble Protein Analyses[6]				X					X[8]	X		X		X	X		X		X	X		X	X		Section 8.6.2
Liquid Biopsy (Blood Plasma)				X					X[3]								X[7]		-					X	Section 8.6.3
Cell Phenotyping and Functional Assays				X					X					X	X		X		X	X		X	X	X	Section 8.6.4
Patient Reported Outcomes																									
EQ-5D-3L				X															X		X	X	See footnote [9]		Section 8.7.1
EORTC-QLQ-C30 (Cohort 2 only)				X															X		X	X	See footnote [13]		Section 8.7.2

[1] Screening Visit 2 assessments should be completed within 28 days of leukapheresis; CT/ MRI scans and ECHO/MUGA scans, performed as standard of care within 4 weeks prior to Screening Visit 2 (prior to study consent) are acceptable. Cytogenetic confirmation of diagnosis can be historic, done as standard of care or be done any time after signing Treatment Consent and does not need to be within 28 day screening window.
[2] Measured pre-infusion, and at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started
[3] Pre-infusion
[4] Screening MRI within 4 weeks of leukapheresis, Baseline MRI within 4 weeks of lymphodepletion
[5] If CMV seropositive at screening, CMV-PCR done at baseline. All CMV seropositive subjects will continue to be monitored by CMV PCR at day 1, week, 2, 4, 6, 8
[6] 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
[7] Can be taken anytime between Week 3 and Week 8
[8] Day 1 samples taken pre-infusion and 2-4 hr. post-start of infusion
[9] EQ-5D-3L will also be done at Month 12 if the subject remains in the interventional phase of the study
[10] Only for a subject who has previously received a gene therapy using a lentiviral vector. Subject's must have results below the LLQQ for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening
[11] Fludarabine dose must be adjusted for renal impairment using the Cockcroft-Gault equation/methods described in Section 6.2.1
[12] Patients that provide a buccal swab sample may also need to provide a confirmatory blood sample for HLA testing
[13] EORTC-QLQ-C30 is for Cohort 2 subjects only; EORTC-QLQ-C30 will also be done at Month 12 if the subject remains in the interventional phase of the study
[14] On study scans from Week 4 through Week 16 should be at least 28 days apart to ensure compliance with RECIST 1.1 requirement for confirmatory scans in the event that an objective response is noted by central read

1.3.2. Long Term Follow Up Phase Time & Events Table

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

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 Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.2
Mutagenic agents, other investigational agents or anti-cancer therapies	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 8.4.11
Clinical chemistry	X	X	X	X		X		X		X		X	X	Section 8.4.12
Vector Copies (Persistence)	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.22
VSV-G DNA (RCL)		X	X	X		X		X		X		X	X	Sections 8.4.23

2. INTRODUCTION

2.1. Study Rationale

2.1.1. Rationale for using MAGE-A4 TCR in synovial sarcoma and myxoid/round cell liposarcoma

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

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

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

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-A2M4 are autologous CD4 and CD8 positive T cells that have been transduced with a self-inactivating lentiviral vector expressing a high affinity MAGE-A4 specific T cell receptor (TCR). MAGE-A4 is a cancer/testis antigen (CTA) that has restricted expression in normal tissue, and is expressed across a range of solid tumors at varying frequencies.

ADP-A2M4 recognizes the MAGE-A4230-239; GVYDGREHTV peptide derived from the MAGE-A4 family of CTAs. Thus, ADP-A2M4 incorporates an affinity enhanced TCR capable of recognizing the human leukocyte antigen (HLA)-A*02-GVYDGREHTV antigen complex.

The safety of ADP-A2M4 has been shown in subjects with different tumor types in an ongoing Phase 1 study (NCT03132922). Data of another genetically engineered T cell investigational product, NY-ESO^{c259}T, in synovial sarcoma provides evidence that TCR therapies can be effective in solid tumors [D'Angelo, 2018a].

2.2. Background

2.2.1. MAGE-A4 background

The cancer/testis antigens (CTA) comprise a number of genes that have restricted expression to the testis, but have been identified by their expression in various tumor types [Caballero, 2009]. These include NY-ESO-1, MAGE-A family, SSX2, BAGE, GAGE, and CT7 among others.

Most of these testis-specific genes are coded on the X chromosome. Several of these antigens, including MAGE-A3, MAGE-A10 and MAGE-A8, also have expression in placenta [Caballero, 2009]. In general, melanoma, ovarian cancer and lung cancer, particularly of the squamous cell type, have the highest frequency of RNA expression across the CTAs. Epithelial cancers such as breast, bladder and prostate cancer have intermediate expression, with frequency of mRNA expression in the range of 30% to 50%. CTAs often have coordinated expression, with several expressed in a single tumor [Gure, 2005]. In addition to RNA, immunohistochemistry is often used to determine the expression levels of CTAs. While it is generally seen that mRNA expression of these antigens correlates well with protein expression it should be noted that there is frequently heterogeneous expression of protein across the tumor, with strong expression in a small subset of tumor cells. There is also epigenetic and post-transcriptional modification that determines protein expression levels under certain conditions.

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

MAGE-A4 has been described as having high expression in synovial sarcoma and MRCLS. A recent study showed that 82% of synovial sarcoma samples expressed MAGE-A4 when evaluated by Immunohistochemistry (IHC) and high expression of NY-ESO-1 and MAGE-A4 was significantly correlated with the presence of necrosis and advanced clinical stage [Iura 2017a]. [redacted] A further report suggested that 67.7% of MRCLS samples, express MAGE-A4 [Iura 2017b]. [redacted]

2.2.2. Discovery of ADP-A2M4

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

The Investigational Product (IP) is comprised of autologous CD4 and CD8 T cells obtained from eligible subjects who have MAGE-A4 expressing tumors and who are HLA-A*02 positive. Subjects who are HLA-A*02:05 are excluded because alloreactivity has been observed in vitro with ADP-A2M4 to this HLA allele. The T cells undergo self-inactivating (SIN) lentiviral transduction with ADP-A2M4 specific nucleic acid under Good Manufacturing Practice (GMP) conditions. The resulting polyclonal ADP-A2M4 specific peptide enhanced affinity receptor (SPEAR™) T cells are now genetically engineered to target the antigen on the subject's MAGE-A4 positive advanced tumor.

2.2.3. Synovial sarcoma/MRCLS current therapies and Emerging Data from ADP-A2M4 and other TCRs

Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

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

Synovial Sarcoma

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

Surgery is the standard therapy for localized disease. Patients with advanced synovial sarcoma receive ifosfamide and/or doxorubicin, as the first-line of therapy [ESMO, 2014]. Doxorubicin-based first-line metastatic doublet therapies, such as doxorubicin in combination with the anti-

PDGFR alpha monoclonal antibody olaratumab [Lilly, 2019], have not demonstrated improved clinical benefit compared to single-agent doxorubicin.

There is no specific standard of care (SoC) in second line therapies and beyond. Pazopanib is approved in the U.S and in Europe for patients with synovial sarcoma previously treated with chemotherapy [Votrient™ US Prescribing Information, EU SmPC]. A randomized double blind placebo controlled Phase 3 trial of pazopanib was conducted in patients with advanced STS. Overall response rate (ORR) as assessed by Data Safety Monitoring Board (DSMB) for the intent to treat (ITT) population was 4%, median duration of response (DoR) of 9 months, and median progression free survival (PFS) of 4.6 months compared with 1.6 months for placebo (HR=0.35, p<0.001). Median overall survival (OS) was 12.6 months compared with 10.7 months for placebo (HR=0.87; 95% CI: 0.67, 1.12). Only 38 subjects with synovial sarcoma (randomized 2:1) were included in the study with a median PFS of 4.1 months in the pazopanib arm vs 0.9 months for placebo (HR= 0.43; 95% CI 0.19, 0.98). The response rate is not reported by histology [Votrient™ US Prescribing Information, EU SmPC]. In a Phase 2 non-randomized study of pazopanib (EORTC Study 62043), responses as assessed by the Investigator were reported in 5/37 (13%) subjects with synovial sarcoma [Sleijfer, 2009].

The response rate in a retrospective analysis of gemcitabine and docetaxel in patients with synovial sarcoma was 10% [Abouharb, 2014]. Several other agents have shown no appreciable anti-tumor activity in synovial sarcoma; these include many novel classes of agents such as HDAC-inhibitors [Cassier, 2013], IGF-1R antibodies [Pappo, 2014; Olmos, 2010], mTOR inhibitors [Schwartz, 2013], vascular disrupting agents [Blay, 2015] and anti-CTLA4 antibodies [Maki, 2013].

Effective treatment options for patients with advanced relapsed synovial sarcoma are limited. The median survival upon relapse from first-line therapy is approximately 12 months [Minchom, 2010] and the ORR from prospective trials for existing therapies ≤ 13%.

Thirty-eight subjects have received treatment with a single dose of ADP-A2M4 up to 9.9756 x 10^9 transduced cells within the phase 1 ADP-0044-001 study. Synovial sarcoma subjects represent the most frequent tumor type in the study and the majority of the subjects treated in Group 3/Expansion. Of the 16 subjects with synovial sarcoma, most subjects were males (62.5%), most subjects were White (87.5%) and the median age was 49.0 years (range 31 to 76 years). The median ADP-A2M4 dose in synovial sarcoma was 9.28 x 10^9 transduced cells (range: 3.44 to 10 x 10^9). The reported adverse events are consistent with those typically experienced by patients with advanced cancer undergoing cytotoxic chemotherapy or cancer immunotherapy (e.g, cytopenias, fatigue, CRS). The most common AE ≥ Grade 3 occurring in ≥ 25% of subjects with synovial sarcoma were, lymphopenia/lymphocyte count decreased (100%), leukopenia/WBC count decreased (93.3%), neutropenia/neutrophil count decreased (88%), neutropenia/neutrophil count decreased (81. %), anemia/RBC decreased (44%), thrombocytopenia/platelet count decreased (44%), hypophosphatemia (44%), rash (19%), CRS (13%), decreased appetite (6%) and hypotension (6%). Cytokine release syndrome (any Grade) was reported in 88% of the subjects with synovial sarcoma. There was one (1) Grade 5 SAE of prolonged pancytopenia with hypoplastic bone marrow considered possibly related to ADP-A2M4. In subjects with synovial sarcoma, the ORR (confirmed responses) was 44% (95%CI:

16.34, 67.71). The Best Overall Response was PR (7), SD (8), PD (1). Disease control rate was 94% with 11 patients still alive at time of 1-September-2020 data cut-off. Subject responses were durable with a median duration of response of 28 weeks range: 12-72 weeks. [CTOS 2020]. This data supports the continued evaluation of ADP-A2M4 in advanced/metastatic synovial sarcoma.

Myxoid/Round Cell Liposarcoma (MRCLS)

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

Treatment involves the wide surgical excision of the tumor and surrounding tissue. Myxoid round cell liposarcoma may be treated with pre-operative chemotherapy and/or pre-operative or post-operative radiotherapy [NCCN, 2012]. Doxorubicin and ifosfamide are the first line systemic treatment options for patients with metastatic disease. Retrospective analyses in previously untreated patients demonstrated response rates of ~38 - 45% [Jones, 2005; Katz, 2012]. Once patients relapse or develop metastatic disease treatment is aimed at slowing that pace of progression. A variety of therapies are used in the second line setting and beyond although only trabectedin and eribulin are approved. A randomized open label phase 2 study of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma enrolled 270 patients. Patients were randomized to receive either a 24-hour infusion of 1.5 mg/m^2 of trabectedin once every 3 weeks, or a 3 hour infusion of 0.58 mg/m^2 of trabectedin once every week for three weeks of a 4 week cycle. The treatment regimen that was determined to be most beneficial was the 24-hour infusion of 1.5mg/m^2 of trabectedin once every 3 weeks. One hundred and thirty-six patients were randomized to this arm of the study and the ORR was 5.6% [Demetri, 2016].

A subsequent randomized, phase 3, open-label, active-controlled trial comparing trabectedin (n=345) treatment with dacarbazine (n=173) in patients with unresectable, locally advanced or metastatic leiomyosarcoma (73%) or liposarcoma (27%) (dedifferentiated, myxoid round cell, or pleomorphic) and previous treatment with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen demonstrated an overall response rate (ORR of 9.9% (CI 0.72, 3.2) with trabectedin, an improvement of median progression-free survival (PFS) of 5.6 vs 1.5 months on dacarbazine but no difference in overall survival [Demetri, 2016]. Eribulin demonstrated an improvement in survival (median OS 13.5 vs 11.5 months; HR= 0.768; 95% CI, 0.618; 0.954) compared with darcarbazine in subjects with liposarcoma and leiomyosarcoma who received 2 or more prior lines of therapy. There was no difference in PFS and ORR was 3.9% with Eribulin and 4.9% with darcarbazine in all patients enrolled. In patients with liposarcoma the response rate was 1.4% [Schöffski, 2016]. Despite the approval of these two agents, overall survival in patients with relapsed disease remains 12-13 months [Demetri, 2016; Schöffski, 2016] and the ORR from prospective trials for existing therapies is < 10%.

A TCR T-cell product targeted against the NY-ESO-1 cancer testis antigen has shown potentially promising clinical activity in eight MRCLS subjects [D'Angelo, 2018b]. For MAGE-A4, in Study ADP-0044-001, two MRCLS subjects were dosed with ADP-A2M4 cells. At the time of Data cut-off, 1 Sept 2020, no MRCLS subjects had responded to ADP-A2M4. ADP-A2M4 was however safe and well tolerated in MRCLS subjects in this phase 1 trial.

2.3. Benefit: Risk Assessment

The results of clinical and non-Clinical studies conducted with ADP-A2M4 cells are summarized in the ADP-A2M4 Investigator's Brochure. This section outlines the potential benefits, risks and the overall benefit: risk for this study.

2.3.1. Benefit

Although the basis for including both synovial sarcoma and MRCLS subjects in Cohort 1 of this study was the reported high frequency of MAGE-A4 expression in both synovial sarcoma and myxoid liposarcoma [Iura, 2017a; Iura, 2017b] as well as the historical clinical activity of the NY-ESO-1 TCR in both synovial sarcoma and MRCLS, preliminary evaluation of MRCLS response and MAGE-A4 antigen status in both the ADP-0044-001 and Cohort 1 ADP-0044-002 studies would suggest that ADP-A2M4 is not as clinically active in MRCLS as it is in synovial sarcoma possibly because of a comparatively lower MAGE-A4 antigen score distribution.

For these reasons, Cohort 2 will only enroll subjects with synovial sarcoma as such patients are likely to derive the greatest therapeutic benefit from the ADP-A2M4 cell product especially since study ADP-0044-001 has shown an ORR of 44% in sixteen heavily pre-treated metastatic synovial sarcoma subjects who had a median of three prior lines of treatment [CTOS 2020]. This data from study ADP-0044-001 in combination with emerging efficacy findings for synovial sarcoma subjects in Cohort 1 of study ADP-0044-002 would indicate that ADP-A2M4 is a promising cell product in metastatic synovial sarcoma especially since there is no specific standard of care beyond first line ifosfamide and/or doxorubicin for patients with advanced (inoperable)/metastatic synovial sarcoma.

2.3.2. Risk

The safety and tolerability of ADP-A2M4 is being assessed in a Phase 1 trial (study ADP-0044-001) across multiple tumor types and in the ongoing Cohort 1 of study ADP-0044-002 including synovial sarcoma and MRCLS. Toxicities observed with ADP-A2M4 are common to other TCR or CAR-T therapies or standard of care chemotherapies.

Toxicities such as CRS, ICANS and pancytopenia/aplastic anemia are specific to TCR and CAR-T therapies and therefore guidelines for management of these events are included in Section 10.5. An advantage of TCR therapy is that they are generally administered once, and the vast majority of toxicities resolve within 4 to 6 weeks after T cell infusion.

Alloreactivity, whereby TCRs reactive towards a given peptide-MHC complex display cross-reactivity towards different HLA allelic variants, is a theoretical risk. Pre-clinical data indicate strong anti-HLA-A*02:05 alloreactivity, making A*02:05 an exclusion allele. Data also indicate

decreased potency against MAGE-A4230-239 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-A2M4 and 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: 1) extensive preclinical evaluation of the ADP-A2M4 which has incorporated learnings from other adoptive T cell therapy programs [ADP-A2M4 Investigator 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 cytokine release syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and pancytopenia/aplastic anemia as well as preventive measures for infectious complications, and 6) a Data Safety Monitoring Board (DSMB) to evaluate safety during the course of Cohort 1.

The potential risks for Cohort 2 (synovial sarcoma only) are expected to be similar to the emerging safety profile in Cohort 1 of study ADP-0044-002, as well as similar to the safety profile reported in the sixteen synovial sarcoma subjects previously dosed in the phase 1 trial, study ADP-0044-001 [CTOS 2020]. Moreover, when combined with the emerging safety profile in Cohort 1, the additional 45 synovial sarcoma subjects in Cohort 2 will permit a more deeper understanding and a better estimate of the frequency of adverse events of special interest (AESI) i.e. incidence of CRS, ICANS and pancytopenia in synovial sarcoma subjects treated with ADP-A2M4 cells compared to safety data from Cohort 1 alone.

2.3.3. Overall benefit: risk conclusion

In Cohort 1, based on the initially promising emerging efficacy and safety findings from the Phase 1 ADP-A2M4 SPEAR™ T-cell trial (study ADP-0044-001), it was justifiable from a benefit-risk perspective to treat subjects with both advanced synovial sarcoma and MRCLS as they each constituted patient populations with a high unmet medical need, albeit with distinctly different metastatic disease natural histories. However, as more mature data has accrued from study ADP-0044-001 in combination with emerging findings from Cohort 1 of this ongoing Phase 2 trial (see Section 4.2., below), it has become apparent that ADP-A2M4 cells may potentially be less clinically active in MRCLS compared to synovial sarcoma. Therefore, at this time, continued evaluation of ADP-A2M4 treatment in Cohort 2 is only justifiable for synovial sarcoma subjects from a therapeutic benefit perspective. In regard to mitigation of risks, measures to ensure safe administration of ADP-A2M4 have been included in this study protocol, with close monitoring for toxicities and guidelines for their management.

The potential risks identified in association with ADP-A2M4 are justified by the anticipated benefits which may be afforded to patients with advanced (inoperable)/metastatic synovial sarcoma in Cohort 2. Indeed, real-world evidence in metastatic synovial sarcoma suggests that

pazopanib - which is approved for 2nd-line metastatic soft tissue sarcoma treatment in the United States and Europe - is not the most frequently administered 2nd-line therapy at several major synovial sarcoma centres in the United States possibly because of its low ORR [Pollack, 2020]. Therefore, this provides a unique therapeutic opportunity for ADP-A2M4 to potentially become the first licensed cell therapy product in post-1st-line advanced (inoperable)/metastatic synovial sarcoma if the overall benefit-risk findings from this phase 2 trial (study ADP-0044-002) are favorable.

3. OBJECTIVES AND ENDPOINTS

Objectives	End Points
Primary:	
To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review in Cohort 1
Secondary:	
To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	For Cohort 1 and across Cohorts (overall): • 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-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review across Cohorts (overall) For Cohort 1 and across Cohorts (overall): • Time to Response (TTR) • Duration of Response (DoR) • Best Overall Response (BOR) • Progression Free Survival (PFS) • Overall Survival (OS)

Development and validation of an in vitro diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Across Cohorts: • Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay
Characterize the in vivo cellular pharmacokinetics (PK) profile of ADP-A2M4 cells	For Cohort 1 and across Cohorts (overall): • Peak persistence and other relevant PK parameters of ADP-A2M4 cells
[redacted]	
[redacted]	[redacted] • [redacted] • [redacted] • [redacted] [redacted] • [redacted]
[redacted]	[redacted] • [redacted] • [redacted]
[redacted]	[redacted] • [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2 single arm, open label study of genetically engineered ADP-A2M4 in HLA-A*02 subjects with MAGE-A4 expressing metastatic or inoperable (advanced) synovial sarcoma or myxoid/round cell liposarcoma (Cohort 1 only). Only subjects with advanced synovial sarcoma will be eligible for Cohort 2. The study consists of two separate, independent, serially enrolled subject cohorts: Cohort 1 and Cohort 2.

Enrollment into Cohort 1 is expected to continue for approximately 12 months and is close to completion at the time of this amendment. Forty-five subjects have been enrolled and 26 subjects have been treated with ADP-A2M4 to date. Enrollment will continue to ensure that at least 45 subjects are dosed in Cohort 1. Dosing is expected to be complete in Cohort 1 in March 2021. Data from subjects in Cohort 1 only will be used for the primary study endpoint and primary statistical analysis.

The clinical and scientific rational for including Cohort 2 is to provide an expanded safety and efficacy data set overall in inoperable (advanced)/metastatic synovial sarcoma to supplement the primary assessment for Cohort 1 subjects who were previously enrolled in Cohort 1 may not enroll into Cohort 2.

4.1.1. Pre-screening

Subjects will sign a Pre-screening Informed Consent Form (ICF) and undergo initial screening for the relevant HLA 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 consent in accordance with IRB/IEC approved processes and any local requirements in advance of providing subjects with a HLA buccal/ cheek swab test and/ or sending tissue for MAGE-A4 testing.

4.1.2. Screening

Subjects who have pre-screened 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 the study. Screening assessments should be completed within 28 days of leukapheresis; CT/ MRI scans and ECHO/MUGA scans, performed as standard of care within 28 days prior to Screening Visit 2 (i.e. prior to treatment consent) are acceptable. Cytogenetic confirmation of diagnosis can be historic, done as standard of care, or be done any time after signing Treatment Consent and does not need to be within 28-day screening window.

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-A2M4 cell Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation.

Anticancer therapy may be administered between screening and leukapheresis, and between leukapheresis and the start of lymphodepletion (bridging therapy), if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods must be adhered to (see Section 5.3). Subjects must be ready to receive IP as the next treatment once manufacturing and any mandatory washout periods are complete even if they remain stable on bridging therapy, provided they have measurable disease per RECIST v1.1.

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

Once the ADP-A2M4 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5) (Section 6.2) followed by infusion of ADP-A2M4 cells on Day 1 (Section 6.3). The lymphodepleting chemotherapy may be given as an outpatient treatment or subjects may be hospitalized at the discretion of the Investigator. The T cell infusion will be given as an inpatient procedure. Subjects will remain hospitalized for observation for at least 10 days post T cell infusion. 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.

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 local and independent review 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’), disease progression will not be determined before 4 weeks (28 days) post infusion of ADP-A2M4 unless there is unequivocal clinical evidence of deterioration. Therefore, imaging scans should not be performed earlier than 4 weeks (on or after 28 days) post infusion.

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 adverse events in accordance Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements for gene therapy clinical trials [FDA, 2006a; FDA, 2010; EMA, 2009].

Subjects will be seen in the clinic for evaluation according to Main T&E Table 1 (Section 1.3.1) until disease progression. Thereafter, subjects will undergo assessments/procedures according to the LTFU T&E Table 2 (Section 1.3.2). The timepoint at which the subject switches to the LTFU assessments/procedures will be driven by the timepoint at which the subject progresses e.g. if there is disease progression at Week 12, the next visit would be due at Week 24 (Month 6).

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

4.2. Scientific Rationale for Study Design

This is a Phase 2 single arm, open-label study with ADP-A2M4 cells for the treatment of subjects with advanced synovial sarcoma or MRCLS who are HLA-A*02 positive and have tumors that express MAGE-A4.

MAGE-A4 is a cancer testis antigen that is highly expressed in synovial sarcoma and MRCLS tumors making it an attractive target. Preliminary clinical evidence in Study ADP-0044-001 has shown an ORR (confirmed responses) of 44% (95% CI: 16.34, 67.71) in advanced (inoperable)/metastatic synovial sarcoma with a disease control rate of 94% including 11 out of 16 patients who were still alive at time of 1-September-2020 data cut-off. Synovial sarcoma responses were durable with a median duration of response of 28 weeks (range: 12-72 weeks). [CTOS 2020]. This ORR is considerably superior than response rates reported with agents currently being used as 2nd line therapies for soft tissue sarcoma (Section 2.2.3).

On this basis, this Phase 2 study (ADP-0044-002) will be a single arm, non-comparative study with a primary efficacy endpoint of Overall Response Rate (ORR) per RECIST v1.1 by independent review in 2 Cohorts where the primary study endpoint will be evaluated in Cohort 1. The historical ORR for post first-line metastatic soft-tissue sarcoma patient populations ranges from 4%-13% (Section 2.2.3). To account for the potential variability in historical control response rate, a more conservative historical ORR of 18% has been estimated for therapies administered in the post 1st-line metastatic synovial sarcoma setting, and will be used to evaluate the efficacy of ADP-A2M4 by hypothesis testing (Section 9).

At the time of this Protocol Amendment (05FEB2021) the ADP-0044-002 study has been enrolling subjects for approximately 12 months. Fifty-three subjects have been enrolled, and 31 subjects have received treatment with a single dose of ADP-A2M4 in Cohort 1 including 27 subjects with advanced (inoperable)/metastatic synovial sarcoma and 4 subjects with MRCLS. Follow-up is ongoing in these three MRCLS subjects, but preliminary evaluation of therapeutic benefit in MRCLS subjects across both the ADP-0044-001 study (2 subjects) and ADP-0044-002 study (4 subjects) would suggest no discernable evidence of an early therapeutic response to ADP-A2M4 cell treatment in MRCLS. For this reason, Cohort 2 in study ADP-0044-002 will only enroll patients with advanced/metastatic synovial sarcoma.

The clinical and scientific rationale for including Cohort 2 is to provide an expanded safety and efficacy dataset overall for metastatic or inoperable (advanced) synovial sarcoma to supplement the primary assessment for Cohort 1.

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 of HLA-A*02:01, A*02:03 or HLA-A*02:06. HLA-A*02 alleles having the same protein sequence as these alleles in the antigen-binding domains (P group) will also be included. 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.

Due to the risk of alloreactivity subjects positive for HLA-A*02:05 in either allele are ineligible. Subjects with HLA-A*02 alleles having the same protein sequence as HLA-A*02:05 in the antigen binding domains (P groups) will also be excluded. Other alleles may be exclusionary after consultation with the sponsor. HLA eligibility testing will be done via Adaptimmune designated central laboratory.

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 high proportion of subjects expected to be excluded based on HLA status, an optional buccal swab kit may be offered to subjects during pre-screening 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 associated instructions would be sent to potential subjects who have provided written 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 screening.

4.2.1.2. MAGE-A4 Expression in Tumor

MAGE-A4 expression was reported in synovial sarcoma (82%) and myxoid liposarcoma (68%) cases [Iura, 2017a; Iura, 2017b]. ADP-A2M4 cells have been shown to produce strong IFNγ responses against tumor cell lines (derived from non-small cell lung cancer, prostate carcinoma, melanoma and ovarian carcinoma) expressing high MAGE-A4 mRNA levels (>10,000 MAGE-A4 transcripts). In addition, ADP-A2M4 cells elicited a strong IFNγ response against a primary melanoma tissue material expressing high MAGE-A4 mRNA and protein expression levels. Since no adequate models to define the threshold of ADP-A2M4 cell activation are currently available, this protocol will select for subjects with high MAGE-A4 expression. As such, Adaptimmune will be using a conservative cutoff (≥2+ in ≥ 30% of tumor cells) to ensure sufficient expression of the antigen.

To ensure that the subject's tumor has the potential to be targeted by the ADP-A2M4 cells, the tumor specimen will be screened at a central reference laboratory for the expression of MAGE-A4 by IHC using a Clinical Laboratory Improvement Amendments (CLIA)-validated Clinical Trial Assay.

Optional remote consent to MAGE-A4 testing is permitted for any clinical site that has the necessary written consent processes in place and has obtained the relevant IRB/IEC and local

approvals. This allows subjects with archival specimens available to consent for MAGE-A4 testing without requiring travel to a clinical study site.

4.2.2. T Cell Manufacturing

ADP-A2M4 is autologous CD4 and CD8 T cells engineered with an affinity-enhanced TCR to target the tumor antigen MAGE-A4. Autologous T cells are obtained from eligible subjects who have MAGE-A4 positive tumors and who have appropriate HLA-A. The CD4 and CD8 T cells are transduced with a SIN lentivirus vector expressing the MAGE-A4 (affinity enhanced clone 1032) under GMP conditions. The product of this transduction is polyclonal T cells which are designed to target MAGE-A4 in tissue. The transfer SIN lentiviral vector has been meticulously designed to contain the genetic elements required for function and for maximum biosafety [Dull, 1998]. Many reports provide evidence supporting the relative biosafety of SIN lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the lentivirus long terminal repeat (LTR) in comparison to the γ retroviral vectors [Montini, 2006; Maruggi, 2009; Modlich, 2009; Montini, 2009].

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

4.2.3. Lymphodepletion

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

Evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia and acute leukemia using adoptive cellular therapy including a CAR showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in a previously cyclophosphamide-only preparative regimen [Turtle, 2015]. Cyclophosphamide was administered at 30 – 60 mg/kg x 1 day and fludarabine at 25 mg/m^2/day x 3 – 5 days. Effective lymphodepletion has also been demonstrated in other CAR-T cell studies using reduced cyclophosphamide dosing, together with fludarabine [Batlevi, 2016].

Data from an open label non-randomized multi-cohort pilot study of genetically engineered NY-ESO-1 SPEAR™ T cells in HLA-A2+ patients with synovial sarcoma (NCT01343043) suggests that fludarabine is an important component of T-cell lymphodepleting regimens and fludarabine 30 mg/m^2 given daily for 4 days in combination with cyclophosphamide may be

associated with more objective responses [D'Angelo, 2018] (see Section 2.2.3). The CD19 CAR-T product tisagenlecleucel also utilizes fludarabine 30 mg/m^2 for 4 days in combination with cyclophosphamide.

The lymphodepleting regimen in this study consists of intravenous fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5).

4.2.4. Long Term Follow-up

Subjects exposed to gene therapies may be at risk for delayed adverse events 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 long term follow up (LTFU) evaluation in the study is designed to adhere to the FDA and EMA guidance for long term follow up of subjects in gene therapy clinical trials [FDA, 2006a; FDA, 2006b, FDA, 2010; EMA, 2009], and involves monitoring subjects who have been exposed to lentivirus-mediated gene transfer in this clinical study for 15 years. Further information on safety monitoring for theoretical risks associated with the use of lentiviral vectors and potential for insertional oncogenesis, as well as safety monitoring are available in Section 10.7, Appendix 7.

4.3. Justification for Dose

The cell dose of ADP-A2M4 is within the range of 1×10^9 to 10×10^9 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 or an additional leukapheresis collection may be 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-A2M4 is being assessed in a Phase 1 trial of multiple tumor types including synovial sarcoma and MRCLS (NCT03132922). Doses up to 9.96 x 10^9 have been well tolerated in this dose escalation study and was associated with a high ORR in 16 advanced (inoperable)/metastatic synovial sarcoma subjects [CTOS 2020].

4.4. End of Study Definition

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

5. STUDY POPULATION

5.1. HLA and Antigen Pre-screening

To be eligible for Pre-screening (Visit 1) subjects must be aged ≥16 and ≤75 years with a diagnosis of advanced (metastatic or inoperable) synovial sarcoma (Cohort 1 or Cohort 2) or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by either histology or cytogenetics. Confirmation of diagnosis by cytogenetics is required prior to leukapheresis.

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 all of the following criteria prior to leukapheresis (i.e. at Screening (Visit 2)) AND prior to lymphodepleting chemotherapy (i.e. at Baseline) to be eligible to participate in this study.

1. Subject (or legally authorized representative) voluntarily agrees to participate by giving written informed consent (and Assent as applicable) in accordance with ICH GCP guidelines and applicable local regulations.
2. Subject (or legally authorized representative) agrees to abide by all protocol required procedures including study related assessments, and management by the treating institution for the duration of the study including long term follow-up.
3. Age ≥16 and ≤75 years at the time the Pre-screening Informed Consent/Assent is signed.
4. Diagnosis of advanced (metastatic or inoperable) synovial sarcoma or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by cytogenetics. Inoperable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise.
    a. For Synovial Sarcoma (Cohort 1 and Cohort 2): confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)).
    b. For MRCLS (Cohort 1 only): confirmation by the presence of the reciprocal chromosomal translocation t(12;16) (q13;p11) or t(12; 22) (q13;q12)
5. Must have previously received either an anthracycline or ifosfamide containing regimen. 1st-line metastatic treatment with ADP-A2M4 is permissible if ifosfamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumor setting. (Subjects who are intolerant of both anthracycline and ifosfamide must have previously received at least one other type of systemic therapy).

6. Measurable disease according to RECIST v1.1.
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 as these alleles in the peptide binding domains (P group) will also be included. Other HLA-A*02 alleles may be eligible after adjudication with the sponsor.
8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥2+ staining in ≥30% of the cells by immunohistochemistry. 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%.
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 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 sexually active subjects are required to use a condom in addition to the female partner use of a highly effective form of contraception or must or must agree to abstain from heterosexual activity with a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide).
13. Must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support) within 7 days prior to lymphodepletion and leukapheresis

Platelets	≥ 100 x10^9/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)
Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)
Coagulation	
Prothrombin Time or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation. Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Renal	
Glomerular filtration rate (calculated CrCl using only the Cockcroft-Gault equation, or measured using either a 24-hr urine creatinine collection or a radionuclide EDTA test) [1]	≥ 60 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with

	direct bilirubin <35% of total bilirubin)
Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT)	≤ 2.5x ULN
[1] 24-hour urine creatine clearance or radionuclide EDTA tests should be used to measure the GFR in all subjects: ≥ 65 years old; clinically obese (≥ 30KG/m2) or underweight (≤18.5KG/m2); borderline low calculated CrCl (Cockcroft-Gault) at approximately 60mls/min (see Section 8.4.10 for further details). **Renal function will be reassessed at baseline using the same methodology.**	

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
Tyrosine kinase inhibitor (TKI) (e.g. pazopanib)	1 week	1 week
Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors,)	4 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 week in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Gene therapy using an integrating vector	Subjects who have received a gene therapy using any DNA-integrating vector other than a lentivirus (retrovirus, AAV, etc.) are excluded from this study. Subjects who have received a gene therapy using a lentiviral vector may be eligible if they have persistence results below the lower limit of quantification (LLOQ) for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.	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 6.5.1 for exceptions.	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 washout period for palliative radiation to non-target organs).

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Major surgery	N/A	4 weeks. A subject must be fully recovered from any surgical 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, 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 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;
    - Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4;
    - Uncontrolled clinically significant arrhythmia;
    - Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months;
    - Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent);
    - Congenital or family history of long QT syndrome;
    - Current uncontrolled hypertension despite optimal medical therapy;

- History of stroke or central nervous system bleeding; transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) in last 6 months;
- Incipient compression/occlusion of a vital structure (e.g. bronchus; superior vena cava; renal outflow tract) which cannot undergo prophylactic stenting;
- COVID-19 infection or a positive COVID-19 RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy. If a subject has a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart.

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 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

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.

5.5. Number of Subjects and Study Duration

Forty-five (45) subjects (90 total subjects) are planned to be dosed separately in this Cohort 1 (synovial sarcoma and MRCLS) and Cohort 2 (synovial sarcoma only). In combination, data from Cohort 1 and Cohort 2 will provide a better, more comprehensive, characterization of the benefit-risk profile in soft-tissue sarcoma patients (especially in synovial sarcoma) than from Cohort 1 alone.

Enrollment into Cohort 1 is expected to continue for approximately 12 months and is close to completion at the time of this amendment. Cohort 2 will begin when dosing in Cohort 1 is completed. Cohort 2 will dose 45 advanced (inoperable)/metastatic synovial sarcoma subjects only and enrollment is expected to continue for approximately 12 months.

The Primary Clinical Analysis will be for Cohort 1 only (i.e. synovial sarcoma plus MRCLS). Clinical cut-off for the primary analysis will occur once the last subject dosed in Cohort 1 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 from Cohort 1 only 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 the study for any reason.

5.6. Sites

The study will be conducted in approximately 24 sites in North America and Europe. The number of centers is necessary to ensure recruitment in this rare patient population. Additional sites may be added at the discretion of the Sponsor.

All sites should have appropriate Medical Emergency / Intensive Care access with provision for beds for study subjects in the event of an emergency. See Table 6: Management Guidelines for Cytokine Release Syndrome and Table 9: Management of ICANS for further guidelines.

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-A2M4.

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

A non-mobilized peripheral blood mononuclear cell (PBMC) collection should be performed by an apheresis unit at the enrolling institution according to the institution's or hospital's policies and procedures. Leukapheresis may be performed at a qualified third-party institution (as may be mutually agreed and approved in advance by both Sponsor and the clinical site), as long as the policies and procedures in place meet or exceed the primary institution's policies and procedures. Bilateral peripheral venous access should be used whenever possible but a temporary central venous catheter (CVC) may be placed for collection if peripheral venous access is inadequate. Standard clinical procedures for apheresis should be followed.

A large volume leukapheresis should be performed. For subjects who are >50 kg, 10 to 15 liters should be processed per procedure; in subjects ≤ 50kg, 2-3 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 calcium chloride and magnesium sulfate 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, may be used by the sponsor for research to modify or improve the manufacturing process and to enhance the clinical response.

6.2. Lymphodepleting Chemotherapy

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

Once the manufactured ADP-A2M4 cell product has been received at the clinical site and the integrity of the bag(s) has been verified by the site, eligible subjects will proceed to have lymphodepleting chemotherapy with fludarabine and cyclophosphamide as described in Table 3.

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 prophylaxis (see Section 10.5.3.7) in line with institutional guidelines.

Appropriate intravenous (IV) hydration should be administered and Mesna should be given to prevent urotoxicity while cyclophosphamide is administered, as described below. Other premedication (e.g. anti-emetics) may also be provided in accordance with institutional standards. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. Based on real-world use of Granulocyte-colony stimulating factor (G-CSF) prophylaxis in Cohort 1 at the study sites, especially those with extensive CD19 CAR-T cell therapy expertise, G-CSF prophylaxis in Cohort 2 synovial sarcoma subjects can be given at the clinical discretion of the Investigator (as per local institutional policy) starting on Day -3 until resolution of neutropenia in accordance with American Society of Clinical Oncology (ASCO) guidelines or institutional practice (see Section 6.2.3).

Table 3: Fludarabine and Cyclophosphamide Treatment Schema

Lymphodepleting Chemotherapy				
Day	**Drug**	**Dose**	**Route**	**Administration**
-7	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[3]
-6	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[3]
-5	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[2]
-4	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
-3	**Start G-CSF**[4]			
-2				
-1				
1	**ADP-A2M4 infusion**[3]			

[1] Fludarabine dose will be adjusted for renal impairment as described in Section 6.2.1
[2] Concentration of 1mg/ml or less
[3] Administration of ADP-A2M4 infusion is described in Section 6.3.
[4] Administration of G-CSF 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
60 – 79 mL/min	20 mg/m^2

Renal function should be estimated using the Cockcroft-Gault Creatinine Clearance (CrCl) equation (no other renal function equations are permitted).

A more sensitive evaluation of renal function using either a 24-hr urine creatinine collection or a EDTA radionuclide test should be performed in subjects at Screening and/or Baseline who are:

- Obese (i.e. BMI ≥ 30 KG/m2
- Underweight (i.e. BMI < 18.5 KG/m2)
- Low borderline CockCroft-Gault calculated CrCl of approximately 60 ml/min.

6.2.2. Mesna

Mesna should be administered according to institutional practice or as recommended below:

- 120 mg/m^2 (20% cyclophosphamide dose) as an IV bolus pre infusion, 4 and 8 hours post infusion on each day of cyclophosphamide administration.

6.2.3. G-CSF

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

6.3. Investigational Product

6.3.1. Premedication

Subjects will be premedicated with antihistamine and acetaminophen/paracetamol 30-60 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.

6.3.2. T Cell Infusion

On Day 1, the subject will receive thawed ADP-A2M4 by intravenous infusion. The T cell infusion will be given as an inpatient procedure and subjects will remain hospitalized for observation for at least 10 days post T cell infusion.

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

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

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

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

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

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

If after thawing the infusion bag is damaged or leaking, the 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 15-45 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 - 250 ml of 0.9% sodium chloride should be connected to the second lumen of the infusion set, used to prime the line, and then the lumen closed. On completion of the infusion of a bag of T-cell product, the main line should be closed and approximately 50ml saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided.

On completion of the cell infusion the set should be flushed using additional saline from the attached bag. If Institutional practice requires a single spike infusion set (e.g. macro drip IV tubing) standard institutional guidelines for the infusion of autologous cell infusion should be followed. The line must be flushed with 0.9% sodium chloride once the infusion is complete. In the event of adverse reaction to the cell infusion the infusion rate should be reduced and the reaction managed according to institutional standard procedures. Steroid treatment should be avoided unless medically required.

In the event a subject develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia (see Section10.5.3).

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.

6.4. Preparation/Handling/Storage/Accountability

6.4.1. Packaging and Labelling

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

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

6.4.2. Receipt and Return

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

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

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 investigational product 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 Investigational Product are correctly received by a responsible person
- Such deliveries are recorded
- Investigational product is handled and stored safely and properly as instructed in the Apheresis and T cell Product Manual
- Investigational product is only administered to study subjects in accordance with the protocol
- Investigational product administration is documented. Records must include the identification of the person to whom the investigational product 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 investigational product 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 investigational product in the trial will be provided with an alert card, which has been previously agreed by the sponsor and approved by the institutional review board (IRB)/ independent ethics committee (IEC). Alert cards will contain at a minimum the name of the subject, the investigator contact number and information regarding the investigational product 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 anticancer locoregional therapies such as non-palliative radiation.

Subjects who undergo any active anticancer therapy, with the exception of surgical resection prior to disease progression, will be considered as having met the 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 ADP-A2M4. However, a subject whose tumor becomes resectable and who undergoes surgical resection prior to disease progression, will continue to be followed for safety and efficacy (progression of remaining lesions, new lesions) in the interventional phase of the study until disease progression is determined. Upon progression, the subject will follow the LTFU schedule. Subjects who have surgery for new lesions consistent with progressive disease or to control progressive disease in previously identified lesions will discontinue the interventional phase and follow the LTFU schedule.

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

The use of systemic steroids may abrogate the effects of the T-cell therapy and therefore use is discouraged unless required to manage CRS (see Section 10.5.6 for CRS treatment recommendations) or other significant immune-mediated adverse events. According to local standard of care or ASCO guidelines, steroids may be used as antiemetics 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. 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 and record the disease progression in the eCRF.

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

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

- All prescription and nonprescription medication, vitamins, herbal and nutritional supplements taken by the subject during the 30 days prior to screening (Visit 2) will be recorded at the screening visit.
- All prior anti-cancer treatments taken by the subject must be recorded regardless of time frame taken
- All concomitant medications taken while subjects are in the interventional phase

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 Immunocompromised 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-A2M4 cell infusion, should be discussed with the Medical Monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Temporary Study Suspension

Throughout the conduct of the study, safety data will be reviewed on an ongoing basis by a Data Safety Monitoring Board (DSMB) see Section 10.2.1. If the following events occur, further enrollment to the study will be suspended and the regulatory authorities informed:

- Any death that is deemed to be at least probably related to the IMP by the Investigator and the Sponsor
- Two or more Grade 4 autoimmune events deemed probably or definitely related to the IMP by the Investigator and the Sponsor
- A subject has a positive RCL:
  - Confirmed positive peripheral blood mononuclear cell (PBMC) replication competent lentivirus (RCL) and no other vector lot is available for use in transduction for subsequent subjects (refer to Section 10.7.2 and Figure 1 on monitoring and management of RCL)
  - Confirmed biological RCL - all ADP-A2M4 cell infusions are halted (see 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
- Died
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- Adverse Event
- Lost to follow-up
- Pregnancy (see Section 10.6.2.1)
- Termination of enrollment by the Sponsor

All subjects ending the interventional phase, with the exception of those who withdraw consent, die, are unable/unwilling to comply with study requirements, are lost to follow up or did not receive any T cells, will switch to the LTFU schedule Table 2, Section 1.3.2 to continue observation for delayed adverse events 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 whole 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 withdrawal of a subject from the study are:

- Unable/Unwilling to comply with study requirements
- Adverse event
- Withdrawal of consent
- Investigator decision
- Lost to follow-up (see Section 7.4)
- Study termination by 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

8.1. Background Assessments

8.1.1. Demographics

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

8.1.2. Disease History

The following information will be recorded in the eCRF: date of initial diagnosis, primary tumor type, anatomical site and size of primary tumor, histology last known stage of disease. Additionally at screening current stage of disease and chromosomal translocations.

8.2. HLA MAGE-A4 Tumor Antigen Testing, and Cytogenetics

There is no window for obtaining HLA, MAGE-A4 antigen and cytogenetic testing 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 approved HLA Sequencing System for Sequence Based Typing (SBT) of Human Leukocyte Antigen (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 subjects' 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 study Sample Collection 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 Sample Collection 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.

8.2.3. Cytogenetics for Diagnosis

For Synovial Sarcoma (Cohort 1 and Cohort 2), a confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)) is required prior to leukapheresis.

For MRCLS (Cohort 1 only), a confirmation by the presence of the reciprocal chromosomal translocation t(12;16) (q13;p11) or t(12; 22) (q13;q12) is required prior to leukapheresis.

Cytogenetic confirmation of diagnosis can be historic, done as standard of care, or be done any time after signing the Treatment ICF and does not need to be within the 28-day screening window.

8.3. Efficacy Assessments

8.3.1. CT/MRI

Imaging scans of the chest, abdomen and pelvis should be performed at Screening, 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 28. 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 independent review, scheduled study 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 8.4.9 regarding brain MRI for safety assessment.

Acceptable imaging modalities for this study include:

- 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 a non-contrast enhanced CT of the chest, if contrast enhanced CT is contraindicated for a subject

- MRI of the extremities if clinically indicated
- 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 inflammation'), disease progression will not be determined before 4 weeks post infusion of ADP-A2M4, 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 not 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-A2M4 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 patient care throughout the study.

8.3.2. Survival

If a subject dies during the study date of death will be recorded in the eCRF. 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 Test in Table 4 describe 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 four 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) in the subject's eCRF.

8.4.2. Physical Examination

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

8.4.3. Prior Anti-cancer Therapies

All 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 recorded on the concomitant medication page of the CRF 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, Appendix 8 for guidance. It is recommended, where possible, that a subject's ECOG be assessed by the same person throughout the study. The frequency of the ECOG assessment is specified in Table 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 only once at Baseline. Weight will be measured according to the frequency specified in Table 1.

8.4.8. Cardiac Assessments

Cardiac assessments will be performed locally at the site.

8.4.8.1. ECG

A single ECG is required. Heart rate, rhythm, PR, RR (if measured/recorded), QRS and QTc intervals will be recorded. QTcB or QTcF is acceptable as per institutional standards but must be consistent from visit to visit.

For Screening (Visit 2) ECGs performed as standard of care within 28 days prior the visit are acceptable. The ECG on Day 1 will be taken before T cell infusion starts.

8.4.8.2. Echo/MUGA

An ECHO or MUGA scan will be performed at screening to determine left ventricular ejection fraction (LVEF) for eligibility. ECHO/MUGA scans performed as standard of care within four 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.

8.4.8.3. Telemetry

For subjects with known cardiac or pericardial tumor involvement at baseline, inpatient telemetry monitoring should be carried out for seven days post-ADP-A2M4 infusion.

8.4.9. Brain MRI

A MRI of the brain with contrast will be obtained at Screening, within 1 month (28 days) of leukapheresis, and Baseline, within 1 month of lymphodepletion, for all subjects. CT with IV contrast may be used only for subjects with contraindications to MRI of the brain. If brain metastases are documented at Screening or Baseline, then *then the subject is not eligible for enrolment onto the study.* If brain metastases are not documented at Screening or Baseline, then dedicated brain CT/MRI scans should be performed as clinically indicated.

8.4.10. Renal Function Assessment

Renal function (estimated or measured glomerular filtration rate (GFR)) will be assessed at Screening using the Cockcroft Gault CrCl. 24-hour urine collection to measure creatinine clearance or by nuclear medicine EDTA measurement should be performed in subjects who are i). clinically obese (i.e. ≥ 30KG/m2); ii). clinically underweight (i.e. ≤ 18.5KG/m2); iii). ≥ 65 years old; iv). Low borderline calculated CrCl ~ 60 ml/min (Cockcroft-Gault).

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

8.4.11. Hematology

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

In years 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 8.4.22) then laboratory assessments may be discontinued.

8.4.12. Clinical Chemistry

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

In years 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 8.4.22) then laboratory assessments are discontinued.

8.4.13. Coagulation

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

Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.

8.4.14. Thyroid Function Tests

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

8.4.15. 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 (see Appendix 4, Section 10.4.5).

8.4.16. Pregnancy Test

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

8.4.17. 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 six 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.

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

8.4.18. CMV PCR

Subjects will be screened for cytomegalovirus (CMV) seropositivity at screening. If seropositive at screening, then CMV-PCR will be done at Baseline. 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, week 2, 4, 6, and 8. See Section 10.5.3.4 for CMV prophylaxis and blood product screening if positive.

8.4.19. ICE Assessment Tool

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

If a subject is thought to have ICANS, the ICE should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated. See Section 10.5.7, Table 7.

8.4.20. C-reactive Protein

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

8.4.21. Ferritin

If cytokine release syndrome is suspected, ferritin levels should be measured approximately every other day with C-reactive protein.

8.4.22. 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 8.6.5).

Samples are required for:

- Safety at Baseline and Week 24, Month 12 and then every 6 months through Year 5 and annually from Years 6-15.
    - 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 may be discontinued.

- 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 (Appendix 7 Section 10.7.3).

- Research at Day 2, Day 4, Day 8, Week, 2, Week 4, Week 8, Week 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 Sample Collection Manual.

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

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

If a positive VSV-G DNA signal is obtained, the study investigator will be informed and the subject will be scheduled for a retest as soon as possible and no later than one month after the initial positive result was reported to the Sponsor. See Appendix 7 Section 10.7.2 for additional information.

Details on collection and shipment of blood sample for RCL is described in the Sample Collection 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, tumor biopsy) until 24 hours afterwards for blood sampling, or until 2 weeks post-biopsy.
- From date of signing the Treatment ICF 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 discontinues the interventional phase of the study. In addition, emerging clinical conditions defined in Appendix 4, Section 10.4.6 will be monitored for starting Day 1. If the subject has not progressed after 12 months, only those emerging clinical conditions defined in Appendix 4, Section 10.4.6 will be collected thereafter.
- During the long-term follow-up phase of the study, subjects will only be monitored for the emerging clinical conditions defined in Appendix 4, 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 Appendix 4.

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.

8.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4, 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 participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 4, Section 10.4.3 .

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt (within 24 hours) notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (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 in the form of Investigator Safety Letters (ISL).

- An investigator who receives an investigator safety letter describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and 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 which 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 investigational product. Details of all pregnancies in female participants and female partners of male participants will be collected from the start of lymphodepletion for as long as there is evidence of T-cell persistence, or until the subject has confirmed disease progression.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6. See Section 10.6.2 for guidance.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

The safety of ADP-A2M4 during pregnancy and lactation has not been established in humans. The target antigen is known to be expressed on fetal germ line tissues and placenta, therefore female subjects who are pregnant, intending to become pregnant, or breast feeding are excluded from ADP-A2M4 studies.

There is no preclinical or clinical trial data of ADP-A2M4 in pregnant women; however, there is a reasonable but unproven likelihood that this intervention may be significantly embryotoxic or even an abortifacient given the underlying biology of the target. The effects on breast milk are unknown, therefore breastfeeding should be discontinued for the duration of the study, starting at the first dose of chemotherapy and for at least 12 months after receiving the investigational product, or four months after there is no evidence of persistence/gene modified cells in the Subjects blood, whichever is longer.

The contraception guidelines provided in Section 10.6.1 should continue to be adhered to during long-term follow up.

A woman who becomes and remains pregnant during the study will be discontinued from the-interventional phase as exposure to radiation from imaging studies would be contraindicated. The subject would follow the LTFU T & E schedule 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. AE of Special Interest

8.5.7.1. Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a potentially life-threatening toxicity that has been observed following administration of antibodies and adoptive T-cell therapies for cancer. It is defined clinically by symptoms which 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 seven 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.

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 grading and management of CRS.

8.5.7.2. Neurotoxicity

Neurotoxicity has been described in association with immune effector cell therapy, and termed immune effector cell-associated neurotoxicity 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 cytokine release syndrome (CRS) symptoms. This form of ICANS tends to be of shorter duration, lower grade (Grade 1–2, see 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 CART-cell therapy, after the initial fever and CRS subside [Lee, 2019].

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

8.5.7.2.1. Monitoring for ICANS

The ICE is a neurological assessment tool which is used to assess cognitive function to monitor for ICANS (see Section 10.5.7 for details). ICE should be measured on the day of ADP-A2M4 infusion prior to receiving treatment and through Day 8 whilst the subject is hospitalized. If the subject is discharged before Day 8 the ICE may be discontinued according to the T&E Table (Section 1.3.1). If a subject is found to have ICANS, the ICE 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. ICE also forms part of the grading system for ICANS developed by [Lee, 2019].

ICANS is graded and managed according to the severity of symptoms, see Section 10.5.7.1 for detailed guidance on management of ICANS.

8.5.8. Long Term Follow Up Adverse Events

During the long-term follow-up (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 Letters 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 (Appendix 7, 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 T&E Table (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]

[redacted]

- [redacted]
- [redacted]

[redacted]

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

[redacted]

- [redacted]
- [redacted]

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

8.6.1. Tumor Biopsy

Baseline biopsy material should be collected within two months of the T cell infusion, with preference for a biopsy to be taken closer to the time of infusion. Tumor tissue should either be taken from non-target lesions or from target lesions where sampling can be done without 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).

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 collected obtained post-progression (e.g. from an excisional surgery).

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

8.6.2. Cytokine and Soluble Protein Analysis

Serum is collected at Baseline, pre-infusion and 2-4 hours post infusion on Day 1 and on Day 2, Day 4, Day 8, Week 2, 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 Sample Collection Manual.

Serum samples may also be used to detect humoral immune responses to tumor antigens and antibodies to ADP-A2M4.

8.6.3. [redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

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

8.6.5. Persistence of ADP-A2M4 TCR+ 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 8.4.22. 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]
- [redacted]

8.7. Patient-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, 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 (VAS) 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 Month 12. Once disease progression is established, the EQ-5D-3L assessment is no longer required.

8.7.2. EORTC-QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed by the Quality of Life Group of the European Organisation for Research and Treatment of Cancer to assess the quality of life of cancer patients.

The EORTC QLQ-C30 will only be used in synovial sarcoma subjects in Cohort 2 at Baseline and post T-cell infusion at Week 8, Week 16, Week 24 and Month 12. Once disease progression is established, the EORTC QLQ-C30 assessment will no longer be required.

The EORTC QLQ-C30 comprises 30 questions. Each of the first 27 questions has 4 levels: Not at All, A Little, Quite a Bit, and Very Much. The respondent is asked to indicate his/her health state by selecting the most appropriate statement. Questions 29 and 30 records the respondent's self-rated health on a horizontal scale where the endpoints are labelled 'Very Poor' and 'Excellent'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

9. STATISTICAL CONSIDERATIONS

The objectives and endpoints for this study are described in Section 3, this section focusses on key aspects for 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). The analysis plan for the objective related to the development of the validated Companion Diagnostic (CDx) will be described in a separate document. Similarly, 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.

The primary analysis will be for Cohort 1 only 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-A2M4) in Cohort 1.

The primary endpoint for efficacy is Overall Response Rate (ORR) in Cohort 1 defined as the proportion of subjects with a confirmed CR or PR relative to the total number of subjects in the analysis population.

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

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

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

- The historical ORR for Synovial Sarcoma ≤13% and for MRCLS <10% (Section 4.2)
- The ORR for historical control that will be used for hypothesis testing in the study will be 18%
- The mechanism of action for the TCR is assumed to be the same for synovial sarcoma and MRCLS.
- Section 2.2.3 states that in subjects with synovial sarcoma, the observed ORR (confirmed responses) for ADP-A2M4 cell therapy was 40.0% at the time of data cut off. Therefore,

for purposes of sample size computation, we assumed ORR for ADP-A2M4 cell therapy would be 40%.

- No formal hypothesis testing is planned for Cohort 2 or across cohorts (overall).

The hypothesis of interest for the primary endpoint is;

(Null Hypothesis) H_0: $p \leq p_0$, vs. (Alternate Hypothesis) H_1: $p > p_0$, where p_0 (historical control rate) = 0.18.

Based on above assumptions, the TCR ORR (i.e., p_1) is set at 0.4. The type I error (α) for this test will be no more than 0.025 and the type II error (β) will not exceed 0.1. Exact Binomial methods will be used to test the hypothesis.

Statistical Design Assumptions:

- The assessment for efficacy will be based on the mITT population using confirmed ORR via RECIST v1.1 per independent review in Cohort 1;
- The type I error (α) for this test will be no more than 0.025;
- The type II error (β) will not exceed 0.1;
- Exact Binomial method will be used to test the hypothesis;
- Cohorts 1 and 2 are independent.

Based on the statistical design assumptions above and the hypotheses and clinical assumptions in Section 4.2, the estimated sample size for the trial is 45 subjects in Cohort 1).

- The ORR for Synovial Sarcoma ranges between 4% – 13% in clinical trials (Section 2.2.3). If we assume that the ORR of the ADP-A2M4 will be 40% (P1), and historical ORR (P0) is 13% a sample size of N=27 provides power to detect an absolute difference of 27% using exact binomial assumptions.

To account for the potential variability in historical control efficacy, a more conservative historical ORR of 18% may also be considered. Using a one-sided alpha=0.025, if we assume that the ORR of ADP-A2M4 will be 40% (P1) and historical ORR may be as high as 18% (P0), a sample size of N=45 in Cohort 1 provides at least 90% power to detect a difference of 22% using exact binomial assumptions.

The following table describes samples sizes for a single cohort under a range of assumptions for the exact binomial assumption as described above.

Historical ORR (P0)	TCR ORR (P1)	Difference (P1-P0)	N
0.13	0.40	0.27	27
0.13	0.45	0.32	21

0.15	0.40	0.25	33
0.15	0.45	0.30	24
0.15	0.50	0.35	19
0.18	0.40	0.22	45
0.18	0.45	0.27	32
0.18	0.50	0.32	21

Based on these evaluations, the sample size for the trial is 45 subjects in Cohort 1 for the primary analysis.

Additional subjects are enrolled in Cohort 2 to supplement Cohort 1 with additional safety and efficacy data based on clinical judgement. No formal hypothesis testing is planned for either Cohort 2 or overall. One benefit of these additional subjects is an increase in precision for ORR by assessing the endpoint across cohorts, and thus in a larger sample of subjects. The following table summarizes the width (point estimate – lower bound) of a 97.5% one-sided confidence interval using exact binomial methods for different sizes of Cohort 2. Also provided for context is the probability that the lower bound of the confidence interval exceeds p0=18% for different sizes for Cohort 2. The assumed TCR ORR is 40%.

Size of Cohort 2	Size of Overall (across cohort)	CI Width	Probability CI LB > 0.18
0	45	0.143	0.916
15	60	0.124	0.959
30	75	0.111	0.989
45	90	0.102	0.994

Based on these evaluations, enrolling an additional 45 subjects in Cohort 2 reduces the width of the confidence interval by about 28% [(0.143-0.102)/0.143] compared to the expected confidence interval width when only using Cohort 1. Further, if the TCR ORR is 40% the probability that the lower bound of the confidence interval exceeds 18% increases from about 92% when only using Cohort 1 subjects to greater than 99% if 45 subjects are enrolled in Cohort 2. These results support enrolling an additional 45 subjects in Cohort 2, for a total of 90 subjects across cohorts.

9.3. Statistical Analyses

The statistical analysis plan (SAP) document will provide full details about data derivations and displays and analysis methods for primary, secondary and exploratory endpoints. This section captures key aspects of the analysis.

Demography and baseline characteristics will be summarized using appropriate descriptive statistics. Subject disposition including number of subjects leukapheresed, lymphodepleted and treated with ADP-A2M4 will be summarized. Reasons for subject discontinuation from the study will be displayed.

9.3.1. Interim Analysis

There is no interim analysis planned.

9.3.2. Efficacy Analyses

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

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

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).

The primary endpoint, ORR per RECIST 1.1. by independent review in Cohort 1, will be evaluated using a one-sided exact-based Clopper-Pearson 97.5% confidence interval (CI). If the lower bound of the 97.5% CI exceeds 18%, the trial has met the pre-specified threshold for demonstrating efficacy and the trial has met the criterion for statistical significance.

As a sensitivity analysis, one-sided 97.5% confidence interval using the Wilson method may also be provided.

ORR per RECIST v1.1 by independent review will also be evaluated across cohorts (overall).

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.
- Duration of Response (DoR), defined as the duration from the initial date of the confirmed response to the date of progressive disease or death.
- Progression Free Survival (PFS), defined as the interval between the date T-cell infusion and the earliest date of disease progression based on RECIST v1.1 or death due to any cause.
- Overall Survival (OS), defined 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 DoR and PFS. As a sensitivity analysis, determination of progression (via RECIST v1.1) using lesion assessments will also be provided.

All secondary efficacy endpoints will be summarized for Cohort 1 and across cohorts (overall).

No hypothesis testing is planned for these secondary endpoints in Cohort 1 or across cohorts. Time to event endpoints (i.e., 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. Two-sided 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.

The following censoring rules will be applied:

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

The proportion of censored observations will be summarized.

The pharmacokinetic (PK) profile 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.

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 also include the per protocol (PP) population. All safety analyses will be summarized for Cohort 1 and across cohorts (overall).

The safety profile will be based on adverse events, serious adverse events, replication competent lentivirus (RCL) and vector integration/clonality. 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.

Adverse events will be summarized using two time periods:

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

Adverse events throughout the trial will be coded by MedDRA v21.0 or higher. The number and percent of subjects reporting any adverse events will be tabulated by system organ class and preferred term. Adverse events 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., cytokine release syndrome (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 electronic Case Report Form (eCRF). Within the EDC system the eCRF data will be entered by the site staff and all source document verification and data cleaning will be performed by the Sponsor or designee (e.g. CRO).

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

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

Standard coding dictionaries, WHO Drug and MedDRA will be used to code medications and adverse events.

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

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

10.1.1.2. Case Report Forms

For each subject enrolled, the completed eCRF must be reviewed and signed by the Principal Investigator or authorized delegate. If a subject discontinues 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, investigational product handling and accountability, presence of required documents, the informed consent process and comparison of eCRFs with source documents.

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

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

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

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and any other site level committee deemed appropriate by the Institution. Approval from each applicable committee will be received in writing before initiation of the study.

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

10.1.3.3. Local regulations/Declaration of Helsinki

The Investigator will ensure this study is conducted in full compliance with the principals of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever, affords the greater protection to the subject. The study must fully adhere to the principles outlined in 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 consent form should be translated and communicated to the subject in a language that is understandable to the subject. Certified translations of the informed consent documentation will be provided as applicable.

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

Tests performed as standard of care prior to documentation of consent may be used for screening results as appropriate (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 (CSR) according to ICH guideline E3: Structure and Content of Clinical Study Reports.

10.1.10. Publication Policy

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

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

10.1.11. Financial Disclosure

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

10.2. Appendix 2: Safety Reviews

10.2.1. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be implemented for this study for Cohort 1 only 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 after approximately 5, 15 and 30 subjects have been dosed. At the time of Protocol Amendment 3, the DSMB has held 2 operational meetings to review data from after dosing of 5, and 15 subjects. Both meetings resulted in the DSMB recommendation to continue the study without protocol modification. The final DSMB meeting will be held after the 30th subject has been dosed in Cohort 1.

A DSMB charter, defining roles and accountabilities and the process for review, is available.

10.3. Appendix 3: Clinical Laboratory Tests

Table 4: Protocol-Required Safety Laboratory Assessments

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

Hematology:	Red blood cell count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Mean cell volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Reticulocytes (absolute) Platelet count White blood cell count (WBC) 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 Creatinine Chloride Glucose BUN or Urea
Other Tests:	Ferritin C-reactive protein

Coagulation Screen:	Prothrombin time (PT) *or* International Normalized Ratio (INR) Activated partial tissue thromboplastin time (aPTT)
Pregnancy Test:	Serum beta-HCG or Urine test
Thyroid Function 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[#] EBV (EBNA)[#] Treponema IgG or RPR [#] Viral reactivation CMV DNA PCR – peripheral blood for detection of reactivation. In the event of suspected end organ CMV disease a biopsy may be required [#] Per Institutional Standard Practice is acceptable

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) ≥ CTCAE grade 3 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 fulfil the definition of an AE or SAE.

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

10.4.2. 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).

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

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. Additional protocol-defined criteria • Any Grade ≥3 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 (see Section 10.4.5): – ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) – ALT ≥3xULN 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 CRF.
- 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 CRF 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 will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. See Section 10.5.6 and Section 10.4.7 for guidance on grading of CRS and ES respectively. For AEs not specifically listed in the CTCAE, The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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.

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.

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.

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 CRF.

- 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 SAE worksheet (SAEW) within 24 hours of the study personnel's discovery of the event.
- Complete the SAEW as fully as possible and obtain the Investigators signature. Create a PDF of the signed SAEW and submit to:
  - [redacted]
  - [redacted]
- Do not delay reporting an SAE if the Investigator is unavailable to sign. Report the SAE as above and provide a copy of the signed SAEW as soon as possible afterwards.

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 Time and Events Table (Section 1.3), and as clinically indicated.

If a Subject meets one of the criteria defined in Table 5, 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 (see Section 1.3). Hepatic safety assessments will be included in this safety follow up.

Table 5: Hepatic Monitoring Criteria

Hepatic Monitoring Criteria	
ALT Absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[1]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[2]	ALT ≥3xULN 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 electronic case report form (eCRF), and a serious adverse event worksheet (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, 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 ≥2xULN	• Viral hepatitis serology[3] • Serum CPK and LDH • CBC with differential to assess eosinophilia • PBMC blood sample for persistence[4] • Assess for the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) and alcohol use • **For bilirubin or INR criteria:** • Hepatologist consultation required • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) • Consider liver biopsy

1. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.
2. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
3. Includes:Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
4. Record the date/time of the PBMC blood sample draw on the CRF. 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, 2006; FDA, 2010; EMA, 2009]. Subjects will be followed according to the schedule outlined in Section 1.3.2 , 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 to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled, and submitted within the annual report of the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days

to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment.

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, cytokine release syndrome, 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 is recommended in all subjects. G-CSF (i.e., filgrastim) should be used for management of neutropenia according to ASCO guidelines [Smith, 2015]. G-CSF should be given on Day -3 until resolution of neutropenia (reaching an ANC of at least 2×10^9/L to 3×10^9/L or as per institutional practice).

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

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-A2M4 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-A2M4 cell infusion.

10.5.3.2. Pneumocystis carinii Pneumonia

Subjects should receive prophylaxis against Pneumocystis pneumonia with drug, dose and duration according to institutional guidelines. Single strength trimethoprim sulfamethoxazole daily is the recommended first line agent, starting at day 28 for one year. Other regimens including atovaquone (1500 mg daily with food) or aerosolized pentamidine (300 mg every four weeks) are also acceptable, e.g. sulfonamide allergy, and 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 HSV episodes.

10.5.3.4. Cytomegalovirus

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. If CMV viremia is detected at baseline, treatment should be initiated and evidence of viral clearance obtained, prior to lymphodepletion chemotherapy. All CMV seropositive subjects will continue to be monitored for CMV viremia by CMV DNA PCR as shown in Table 1 until 60 days post infusion of ADP-A2M4. 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 (300mg daily), entecavir (0.5mg daily), or tenofovir (300mg 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 antifungal 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 x10^9/L, Hb > 8.0 g/dL (or in accordance with institutional practice) and as clinically indicated. See AABB Guideline on platelet transfusion [Kaufman, 2015].

10.5.4.1. 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 allogeneic 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.

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 PI should be contacted and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the ADP-A2M4 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

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 many of which mimic infection including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash and dyspnea. It is important to evaluate the subject for concurrent infections. Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure and disseminated intravascular coagulation. CRS may also be associated with findings of macrophage activation syndrome or occur coincident with tumor lysis syndrome.

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

Table 6 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical, and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels (Section 8.6.2) ferritin (Section 8.4.21), as well C-reactive protein (CRP) (Section 8.4.20) levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 6: Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment	Management Guidelines
1	Constitutional symptoms not life-threatening (e.g., fever, nausea, fatigue, headache, myalgias, malaise)	• Vigilant supportive care[1] • Assess and treat for possible infection[2] • Consider anti-IL-6 therapy[3] (tocilizumab 8 mg/kg* IV) if clinically indicated (i.e., subjects with symptoms persisting ≥ 24 hours or subjects with co-morbidities or subjects of older age)
2	Symptoms require and respond to moderate intervention (Hypotension responds to fluids or one low dose pressor, hypoxia responds to <40% O_2, and/or Grade 2 organ toxicity)	• Monitor cardiac and other organ function • Vigilant supportive care[1] • Assess and treat for possible infection[2] • Treat hypotension with fluid and pressors. • Administer O_2 for hypoxia. • Administer anti-IL-6 therapy[3] (tocilizumab 8 mg/kg* IV at any time if clinically indicated (i.e., subjects with symptoms persisting ≥ 24 hours, or subjects with co-morbidities or subjects of older age)

3	Symptoms require and respond to aggressive intervention hypotension requires multiple pressors or high dose pressors **hypoxia requires ≥40% O^2**, Grade 3 organ toxicity or Grade 4 transaminitis	• Monitor subject very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). • Vigilant supportive care[1] • Assess and treat for possible infection[2] • Treat hypotension with fluid and pressors. Administer O_2 for hypoxia. • Administer anti-IL-6 therapy[3]
4	Life-threatening symptoms Grade 4 organ toxicity (excluding transaminitis)	• Manage subject in ICU • Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required • Administer anti-IL-6 therapy[3]
5	**Death**	

1. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure
2. Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of antimicrobial agents for concurrent bacterial infections, and for treatment of fever and neutropenia as per institutional practice; and antipyretics, analgesics as needed.
3. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first line treatment (tocilizumab 8 mg/kg* IV).

   *The maximum dose for tocilizumab is 800 mg per dose. Corticosteroids can be used for subjects refractory to anti IL-6 therapy. Other immunosuppressor agents may also be used, including TNFα and IL-1R inhibitors. Please see text below for details

Source: Lee, 2019; Neelapu, 2018

For subjects requiring immunosuppressive intervention anti-IL-6 therapy should be the first line treatment. Tocilizumab is a humanized anti-IL-6 receptor antibody that has been approved for the treatment of CRS. Anecdotally, tocilizumab has produced rapid and complete correction of

CRS with single doses [Maude, 2014]. The United States product insert (USPI) for tocilizumab recommends a dose of 8 mg/kg administered over 1 hour in adult subjects as the first-line treatment of severe CRS. Subjects may receive a repeat dose(s) if clinical signs and symptoms do not improve at least 8 hours apart. Refer to Section 10.5.7 below for subjects experiencing Immune Effector Cell-Associated Neurotoxicity Syndrome concurrent with CRS.

Second-line, tocilizumab refractory, management of CRS is at the discretion of the Investigator following local institutional policy. This can potentially include the use of corticosteroids either in combination with a second dose of Tocilizumab [Maus, 2020] or a corticosteroid administered as a single agent after two doses of Tocilizumab have been administered and if CRS symptoms are persisting. Use of steroid sparing agents (e.g. siltuximab or anakinra) is at the discretion of the Investigator.

Lee [2019] recommend steroids as second-line therapy for CRS as the response to anti-IL-6 therapy may be more rapid and owing to the potential of steroids to attenuate the anti-tumor effects of the adoptive T cell therapy. However, in subjects with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability (See Section 10.5.7) or other life-threatening symptomatology, consideration may be given to the use of corticosteroids as immunosuppressive therapy. High doses (e.g. 2 mg/kg/day prednisone equivalent) may be required.

If cytokine release syndrome is suspected, a physician with expertise in the management of subjects following bone marrow transplant should be consulted. If high dose corticosteroids are required, treatment should generally be continued until resolution to Grade 1 followed by tapering doses over several weeks.

Please refer to the most recent version of the product label for tocilizumab and the latest Society for Immunotherapy of Cancer (SITC) guidelines for CRS [e.g. Maus, 2020].

10.5.7. Management of Encephalopathy Syndrome (ES)

See Section 8.5.7.2 for a description of ICANS. Neelapu, et al [Lee, 2019] have developed a grading system for ICANS which incorporates the Immune Effector Cell-Associated Encephalopathy 10-point neurological assessment (ICE) tool, see Table 7. Points are assigned for each of the tasks in Table 7 which are performed correctly. Normal cognitive function is defined by an overall score of 10.

The ICE should be used to monitor all subjects for ICANS.

Table 7: ICE 10-point neurological assessment [based on Lee, 2019]

Task	ICE Points
Orientation to: year, month, city, hospital, and President/Prime Minister of country of residence	Total of 4 points (one point for each)
Naming: Ability to name three objects (e.g. point to: clock, pen, button)	Total of 3 points (one point for each)

Task	ICE Points
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 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 score is used in grading of ICANS as presented in Table 8.

Table 8: Grading of Immune Effector Cell-Associated Neurotoxicity (ICANS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score[1]	7–9	3–6	0–2	0 (patient is unarousable, and unable perform ICE)
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizures	NA	NA	Any clinical seizure, focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with response to intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings [3]	NA	NA	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Elevated ICP/ cerebral edema	NA	NA	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

Source: Based on Lee, 2019

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

[1] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE 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.

10.5.7.1. Management of ICANS

The recommended management of ICANS should be based on toxicity grade. Table 9 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. For subjects with neurologic symptoms refractory to an initial dose of anti-IL-6 therapy, consider siltuximab for the second dose based on its mechanism of action directly against IL-6.

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

Table 9: Management of ICANS

Grade	Treatment
1	For all patients: • Vigilant supportive care; aspiration precautions; intravenous (IV) hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired • Avoid medications that cause central nervous system depression • Evaluate for other contributing causes and treat accordingly Unless symptoms are mild and transient (e.g. 1 point change in ICE for less than 12 hours): • Neurology consultation including funduscopic exam to assess for papilledema • MRI of the brain with and without contrast (CT scan of the brain if MRI is not feasible). Further testing if indicated such as diagnostic lumbar puncture with measurement of opening pressure if increased intracranial pressure is suspected, or MRI spine if the subject has focal peripheral neurological deficits • Institute levetiracetam therapy and consider EEG if seizure activity is suspected • Consider anti-IL-6 therapy with tocilizumab 8 mg/kg[1] IV or siltuximab 11 mg/kg IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent CRS
2	• Supportive care and neurological work-up as described for grade 1 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 patient 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 ES without concurrent CRS; continue corticosteroids until improvement to grade 1 ICANS and then taper • Stage 1 or 2 papilledema with cerebrospinal fluid (CSF) opening pressure <20 mmHg should be treated with a corticosteroid regimen as per Grade 4 below. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 ICANS

Grade	Treatment
4	• Supportive care and neurological work-up as indicated for grade 1 ICANS • Consider neurosurgical consultation for patients with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 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 800mg

10.5.8. Management of Prolonged Cytopenia

10.5.8.1. Definition of prolonged cytopenia, pancytopenia and plastic 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 EU SmPC; KYMRIAH USPI; YESCARTA EU SmPC; YESCARTA UPSI]. 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 a rare hematological disorder and is defined as diagnosis of severe aplastic anemia made in the setting of a hypocellular bone marrow when 2 of the following 3 blood counts are met: Absolute Neutrophil Count < 500/µL, Absolute Reticulocyte Count < 60,000/µL, and Platelet Count < 20,000/µL, with the exclusion of myelodysplastic syndrome.

Subjects may be symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. 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.

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 2mg/kg initial dose) or more aggressive regimens (e.g. antithymocyte globulin (ATG), cyclosporine, eltrombopag) as well as antimicrobial prophylaxis/therapy with the advice of your Hematology/Infectious Diseases consultant(s). If high dose corticosteroids are initiated, duration of therapy and taper should be determined with advice from expert consultants.

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

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

10.5.9.1. Diagnosis of GVHD

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

Table 10: Overview of Clinical Findings/Symptoms of GVHD

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

Of Note: Bone marrow suppression and related cytopenias have been described in the setting of acute GVHD. Management of this complication is challenging, with no clearly established

guidelines regarding immunosuppression. Treatment may be largely supportive, including transfusions and treatment of infections.

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

Bone marrow suppression is also a feature of transfusion-related GVHD

10.5.9.2. Grading of GVHD

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

Table 11: Staging of Dermal, Gastrointestinal and Hepatic Involvement with Acute GVHD

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

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

Table 12: Grading of Acute GVHD

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

[a]Staging is described above
[b]Mild, moderate, or severe decrease in performance status

10.5.9.3. Management of GVHD

Although the diagnosis of GVHD is predominantly based on clinical grounds, biopsy of affected organs can be helpful in excluding other causes and supporting the diagnosis of GVHD with

consistent histopathologic findings. However, awaiting biopsy results should not delay the institution of appropriate therapy.

If GVHD is suspected:

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

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

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

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

Table 13: Management Guidelines for GVHD

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

If high dose corticosteroids are required, treatment should generally be continued for at least 5 days followed by tapering doses over several weeks. A physician with expertise in infectious

diseases in immunocompromised hosts should be consulted, and prophylactic antimicrobials should be considered.

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

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

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

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

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:

- Female subjects of childbearing potential (FCBP) 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.
- Male sexually active subjects are required to use a condom in addition to the female partner use of a highly effective form of contraception or must agree to abstain from heterosexual activity with a female of childbearing potential 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).

Effective methods of contraception include: intra-uterine device, injectable hormonal contraception, oral 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 long-term follow up.

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-A2M4.
- 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)

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

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

10.7.1.2. Insertional oncogenesis

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidance [FDA, 2006a; FDA, 2006b; EMA, 2009]. Insertional oncogenesis is a theoretical risk in T cells transduced with a lentiviral vector. T cells appear resistant to transformation by integrating viruses [Cattoglio, 2010; Newrzela, 2008]. However, there are cases of oncogenesis with γ-retroviral transduced stem cells. Four of nine subjects with X-linked severe combined immunodeficiency (SCID-X1) treated with retrovirus transduced stem cells were found to have insertion near the LMO2 proto-oncogene promoter, leading to aberrant transcription and expression of LMO2 which resulted in acute T-cell lymphoblastic leukemia [Hacien-Bey-Abina, 2003; Hacien-Bey-Abina, 2014]. Additionally, two subjects treated for X-linked chronic granulomatous disease (X-CGD) with retroviral transduced stem cells demonstrated insertional activation of the EVI1 transcription factor which resulted in genetic instability, monosomy 7 and clonal progression toward myelodysplasia [Stein, 2010].

10.7.2. Testing for RCL and Persistence

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. The scheme for RCL testing is presented in Figure 1 below. RCL testing and monitoring will take place on subject's peripheral blood mononuclear cells (PBMCs) which will be collected at Baseline and then at 3, 6, and 12 months post-infusion and annually from year 2-15. Samples will be tested for the presence of VSV-G DNA copies.

If all samples are negative in year one, PBMC samples will be collected and archived annually until 15 years 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. The DSMB will be notified and a review by Adaptimmune's Safety Review Team and Safety Governance Board will take place.

Response to potential outcomes of second test:

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

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

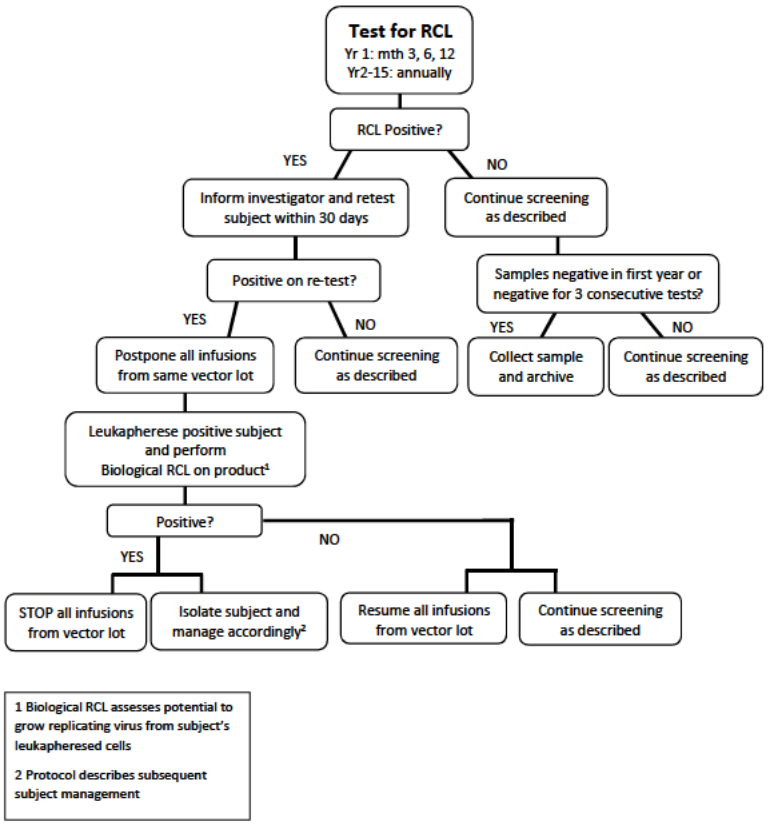
If the biological RCL test is negative, infusions for all subjects can resume.

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

The following approaches have been discussed for subject management:

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

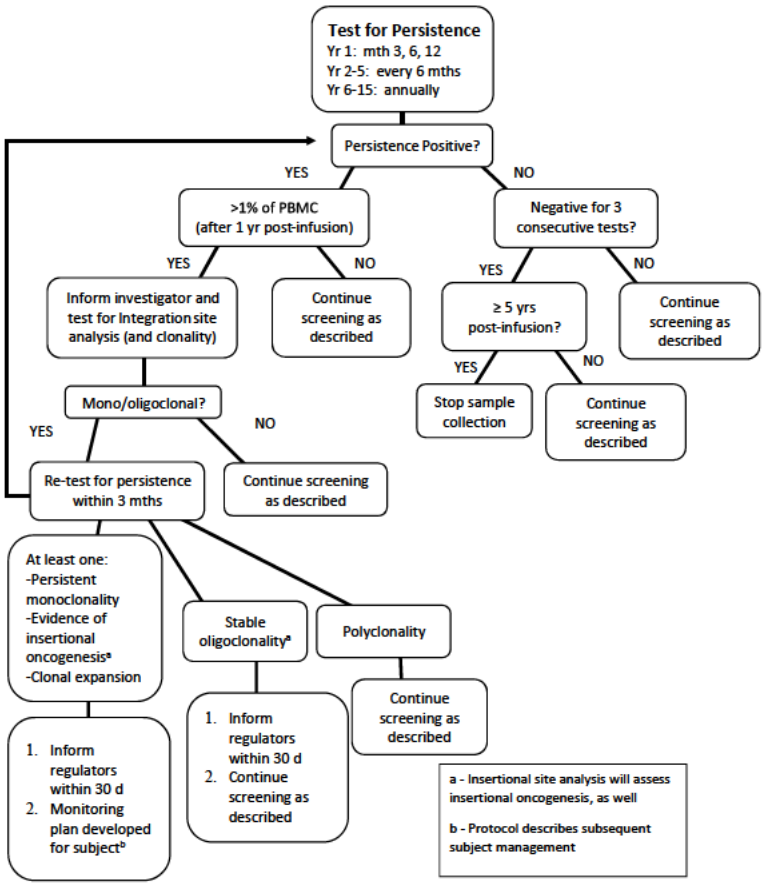
Figure 1: Flow chart for testing for Replication Competent Lentivirus (RCL)



PBMC samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects. Subject samples will be tested for persistence at 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, 2006a; FDA, 2006b; EMA, 2009]. The scheme for testing for persistence is presented in Figure 2.

The samples will be tested using a PCR-based method to detect the presence of the integrated vector sequences Psi DNA, both of which are part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion, greater than 1% PBMCs test positive for vector sequences, the subject's PBMCs will be evaluated for integration site analysis (see 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 insertional oncogenesis.

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

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

monitoring plan specific to the health care risk and strategies to inform appropriate subjects, investigators, FDA and other regulators of the findings.

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

10.7.4. Letter to Physician - LTFU notification

[date]

[name and address]

Dear [physician name],

Your patient [patient name] has participated in a clinical research study, [interventional study name and number], that requires 15 year monitoring for adverse events. To aid in reporting of adverse events that are possible related to the clinical research study, we are asking the patients on our research study to designate a primary care or infectious disease physician that may help in the monitoring and reporting of adverse events. Your patient has designated you. If upon any of your visits with your patient, any of the following events are reported or discovered, please contact the study nurse or physician as soon as possible:

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

If your patient experiences any of these events, please refer them back to their study physician. Please contact the study coordinator below as soon as you can so that they can record the event and then monitor your patient's health if necessary. When you call, remember to mention the protocol number of the study which is ADP-0044-002, patient ID [XXX] and the study title which is "A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma".

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 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 with contrast is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Ultrasound (US) should not be used to measure tumor lesions. The same modality should be used when comparing or making assessments.

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

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

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

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

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

Measurable lesions

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

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

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

Non-target Lesions

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

Evaluation of Target Lesions

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

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

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

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

Special notes on the assessment of target lesions:

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
- Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.
- Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

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

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

Non-CR/Non-PD:

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Special notes on assessing progression of Non-Target lesions

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

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

New lesions

The appearance of new malignant lesions denotes disease progression:

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

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

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

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

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

- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[1]
CR	CR	No	CR	≥4 wks. Confirmation[2]
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation[3]
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. from ADP-A2M4 infusion
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 for further details on what is evidence of a new lesion [Eisenhauer, 2009]
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. Confirmation of response is established by no evidence of disease progression at the subsequent time point. 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 Non-evaluable Designation

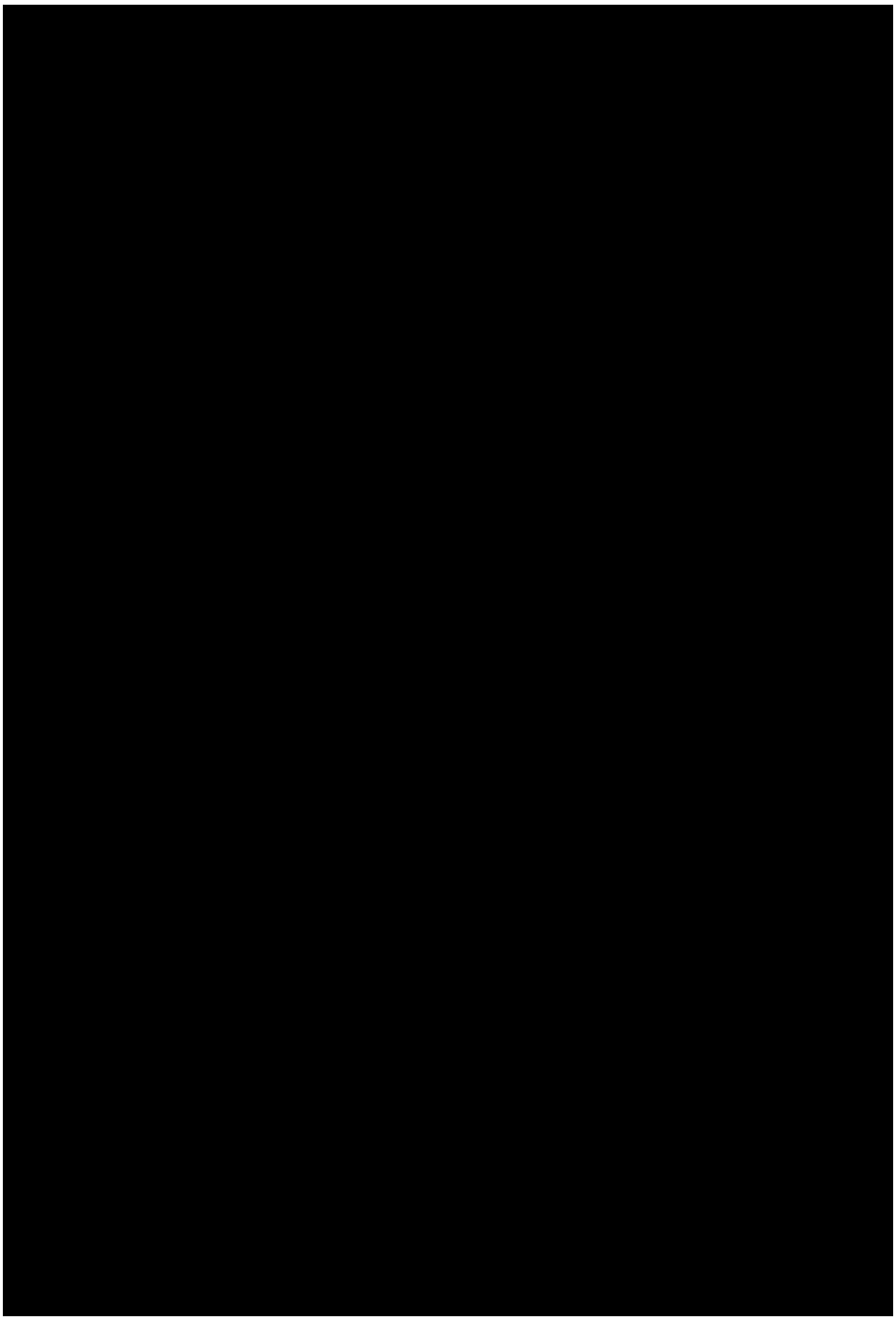
When no imaging/measurement is done at all at a particular time point or the imaging is technically unreadable, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a 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.

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

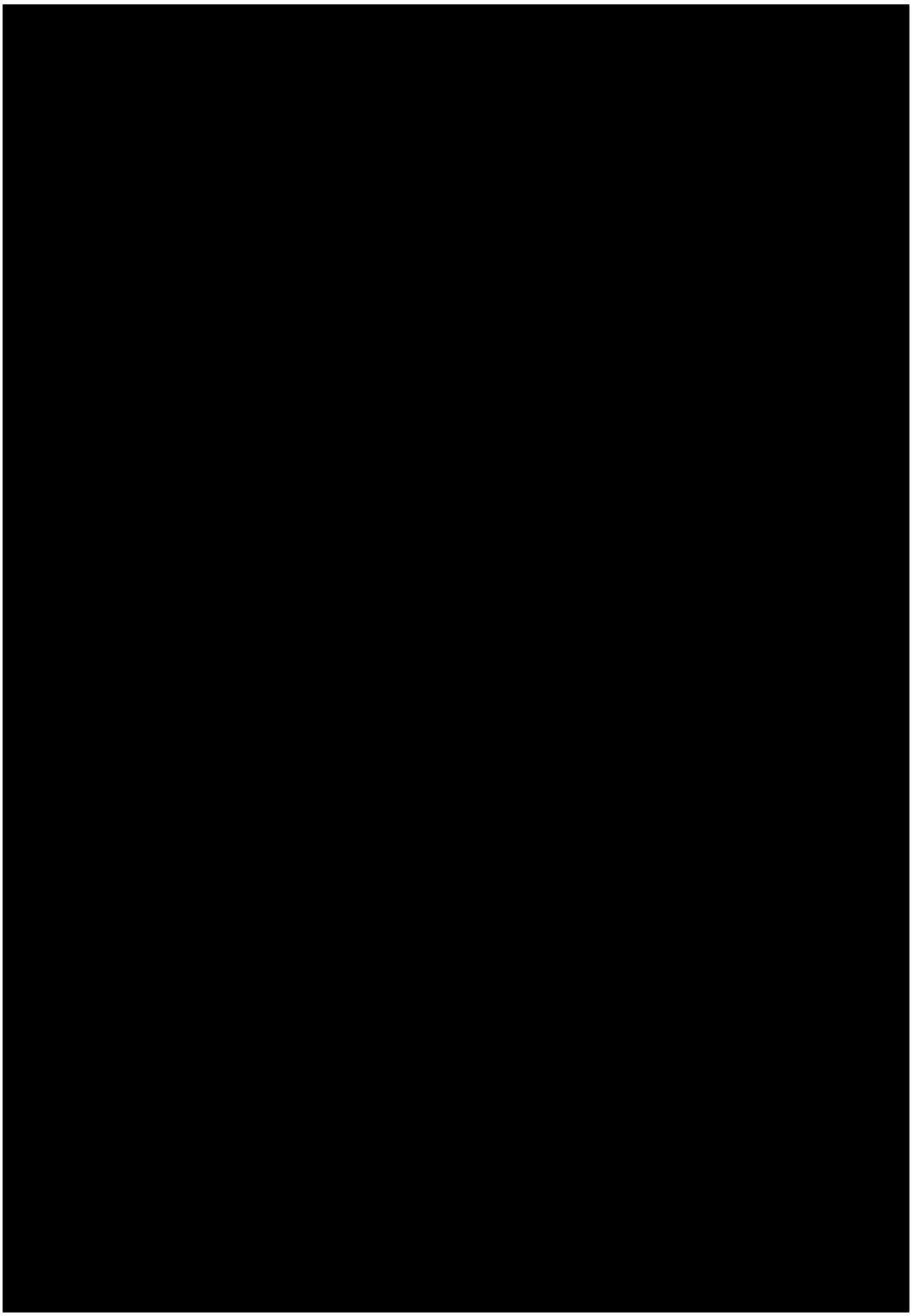
[Oken, 1982]

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



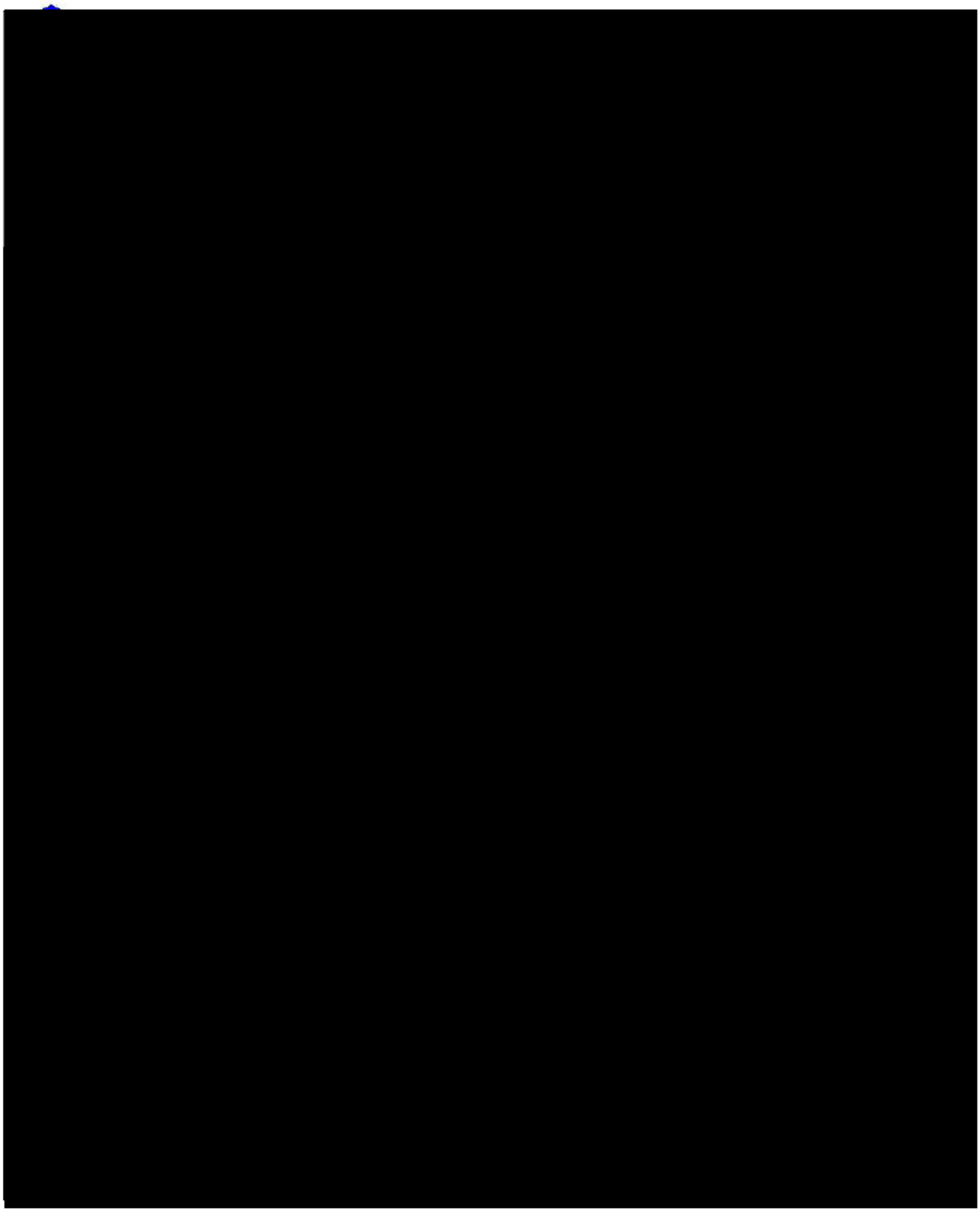
[redacted]

[redacted]



10.11. Appendix 11: EORTC-QLQ-C30 Questionnaire (SAMPLE)

ENGLISH



ENGLISH

[redacted]

10.12. Appendix 12: Abbreviations

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

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

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

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

NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal Investigator
PTT	Partial thromboplastin time
PR	Partial response
qPCR	Quantitative polymerase chain reaction
RAC	Recombinant DNA Advisory Committee
RC	Research Committee
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
RIND	Reversible ischemic neurologic deficit
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
SCID-X	Severe combined immunodeficiency disease – X linked
SD	Stable disease
SGPT	Serum glutamate-pyruvate transaminase
SIN	Self-inactivating
SOP	Standard operating procedure
SPEAR	Specific Peptide Enhanced Affinity Receptor
SPM	Study Procedures Manual
SUSAR	Suspected, unexpected serious adverse reactions
TCR	T cell receptors
TIA	Transient ischemic attack
TILs	Tumor-infiltrating lymphocytes

TKI	Tyrosine kinase inhibitor
TTR	Time to response
TURBT	Transurethral resection of bladder tumor
ULN	Upper limit of normal
VSV-G	Vesicular Stomatitis Virus G glycoprotein
WBC	White blood cell
WHO	World Health Organization
X-CGD	X-linked chronic granulomatous disease

10.13. Appendix 13: Protocol Amendment History

Protocol Version Amendment 2, UK Original (UK-2.0) dated 20MAR2020 is replaced in the UK only by Protocol Amendment 3, UK Version 3.0 (UK-3.0) dated 02MAR2021.

Sections amended	Change	Rationale for change
1.3.1, 6.2.1, 8.4.10	Inclusion of adjustment of fludarabine dose for subjects with renal impairment	Updated to give additional clarification
1.3.1, 3, 8.7.2, 9.3.3, 10.11	Inclusion of EORTC-QLQ-C30 questionnaire for subjects participating in Cohort 2	New questionnaire is to be used In subjects in cohort 2
1.1, 1.3.1, 8.3.1	Clarification that CT/MRI scans conducted between Week 4 to Week 16 should be at least 28 days apart	Conducting scans 28 days apart ensures compliance with RECIST 1.1 requirements
2.2.3	Updated data pertaining to safety and efficacy of ADP-A2M4	Make consistent with current ADP-A2M4 Investigator's Brochure
1.1, 2.1, 2.2.4, 4.1, 4.2, 5.1, 5.2, 8.2.3	Inclusion of Cohort 2 in synovial sarcoma subjects	Include Cohort 2 for synovial sarcoma patients subjects
2.2.4, 2.2.5,	Amended to align with current available data	Aligned with current known data surrounding synovial sarcoma
3, 9, 9.1, 9.2, 9.3.2, 9.3.3	Inclusion of separate Cohorts 1 & 2	Additional cohort has been added to further assess patients with synovial sarcoma
1.1, 4.1, 4.2, 5.5, 9.2	Clarification that first 45 subjects will be included in Cohort 1 and addition of subsequent independent Cohort 2	Language added to clarify how many subjects will be dosed in each cohort
1.1, 3, 9.3.2, 9.3.3	Clarification that the primary efficacy endpoint is Overall Response Rate per RECIST v1.1	Language updated to reflect addition of new cohort and

	by independent review for Cohort 1. Secondary endpoints and safety endpoints were updated to reflect addition of new cohort.	that no new hypotheses testing is required.
4.3	Additional evidence for dose included	Provide evidence for dose range up to 10×10^9
1.1, 5.2	Inclusion criteria expanded for subjects who have previously received anthracycline or ifosfamide	To provide clarification of systemic therapy inclusion
1.1, 5.2	Inclusion laboratory values table updated	Clarification of inclusion criteria based on ANC, Prothrombin Time or INR, and GFR
1.1, 5.3	Exclusion of subjects with incipient compression/occlusion of a vital structure	Included in exclusion criteria following safety event and as recommended by FDA
1.1, 5.3, 10.5.3.1	Addition of COVID-19 requirements	Information added for COVID-19 requirements
6.1	Updated to allow for local leukapheresis	Updated to allow local leukapheresis
6.2	Granulocyte colony stimulating factor (G-CSF) guidance updated	Updated to align with current safety data
6.5.2, 6.5.2.1	Addition of Guidance on COVID-19 vaccinations	Updated to clarify guidance related to COVID-19 vaccinations
8.1.2	Updated to reflect additional information on disease history to be collected in eCRF	Updated to include site and size of tumor as well as last known tumor stage
8.4.8.1	Updated to confirm that QTcB or QTcF are acceptable	Updated to confirm that QTcB or QTcF are also acceptable for collection

8.4.13	Updated to clarify requirements for administration of anticoagulants.	Updated to clarify the need for either a low molecular weight heparin injection or a novel oral anticoagulant
8.6.3	Clarification of timing of Baseline liquid biopsy collection	Updated to include collection at baseline
9.1	Reference to CDx analysis population removed	Removed as information regarding CDx analysis is held outside of protocol
9.1	Reference to PP Population removed	Based on subjects enrolled to date no major protocol violations where subjects will be excluded from primary analysis
9.3.3	Removed reference to QOL exploratory endpoints.	Analysis of exploratory endpoints will be addressed in the Statistical Analysis Plan
10.4.4	SAE reporting updated to remove location of SAEW	Not required to be referenced in protocol
10.5.4.1	Irradiated Blood Product section updated	Updated as per latest guidance
10.5.6	Updated Management of CRS	Updated as per latest guidance
10.5.8	Updated Management of prolonged cytopenia	Updated as per latest guidance
5.2, 9.3.2, 10.2.1, 10.3, 10.4.6, 10.4.7	Administrative	Administrative updates, corrections and clarifications

10.14. References

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ADP-A2M4 (MAGE-A4^{c1032}T) Investigator's Brochure, May 2019

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Study Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

NCT number: NCT04044768

Document: Statistical Analysis Plan

Document Date: 28 Oct 2021

PROTOCOL NUMBER ADP-0044-002

A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

(SPEARHEAD 1 STUDY)

PROTOCOL VERSION: AMENDMENT 3, FRANCE 5.0

DATE: 28OCT2021

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T Cells in Subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma (MRCLS)

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-A2M4 Investigator's Brochure.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T Cells in Subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma (MRCLS)

Product Name: ADP-A2M4

Protocol Number: ADP-0044-002

IND Number: 17235

EudraCT Number: 2019-000589-39

DATE OF ORIGINAL PROTOCOL: 25FEB2019

Amendment Number	Date	Reason for Change
Original	25FEB2019	NA –
Amendment 1	04JUN2019	Change in the lymphodepletion regimen Addition of ECG at Day 5 Added upper age limit Increase entry criteria for ANC, platelets, GFR Additional exclusion criteria under uncontrolled intercurrent illness Emerging data for ADP-A2M4 added Updated study physician Administrative changes
Amendment 1, France (FR) Original (FR-1.0)	22NOV2019	Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) requested change to: - requirement for 7 days hospitalization Administrative changes

Amendment Number	Date	Reason for Change
Amendment 1, France (FR) 2.0 (FR-2.0)	09JAN2020	Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) requested change to: requirement for 10 days hospitalization
Amendment 2, France (FR) 3.0 (FR-3.0)	23JUN2020	Updates and clarifications to HLA criteria Removed futility analysis and associated protocol aspects Updated number of subjects Decreased duration of enrollment Increased LVEF criteria Clarification of washout for prior gene therapy Added updated data from current ADP-A2M4 Investigator's Brochure Update to CRS management guidelines Updated Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells Inclusion of optional remote consent for MAGE-A4 tissue testing and/ or buccal/ mouth swab test for HLA assessment at participating sites Administrative changes and clarifications

Amendment Number	Date	Reason for Change
Amendment 3, France (FR) 4.0 (FR-4.0)	18MAY2021	Update to sponsor contacts Age range updated to include pediatric patients from ≥ 10 years Addition of Lansky assessment in subjects <16 Addition of Cornell Assessment Pediatric Delirium Score in subjects <12 Addition of Cohort 2 (45 synovial sarcoma subjects) Updates to safety and efficacy information to align with current IB Information added for COVID-19 requirements Exclusion for compression/occlusion of a vital structure added Addition of EORTC QLQ-C30 (Cohort 2 only) Addition of PedsQL™ Removal of CDx and PP Population definitions Additional details added throughout for additional clarity of wording Template language updated

Amendment Number	Date	Reason for Change
Amendment 3, France (FR) 5.0 (FR-5.0)	28OCT2021	Update to inclusion criteria Addition of SRC for subjects < 16 years old Update to blood volume collection to comply with European recommendations for pediatric subjects

CONFIDENTIALITY STATEMENT

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

[redacted]

[redacted]

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]
Secondary Sponsor Study Physician	[redacted]	[redacted]	[redacted]	[redacted]

Sponsor Details:

Adaptimmune LLC
351 Rouse Blvd
Philadelphia, PA 19112
USA

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma	
Short Title	SPEARHEAD 1 Study
Protocol Number	ADP-0044-002
Phase	2
Methodology	Subjects with advanced synovial sarcoma or myxoid/ myxoid round cell liposarcoma (Cohort 1 only) will be Pre-screened to determine appropriate human leukocyte antigen (HLA) and tumor antigen status. Only subjects with advanced synovial sarcoma will be eligible for Cohort 2. Only subjects expressing at least 1 HLA-A*02 inclusion allele and no exclusion allele and whose tumor expresses the MAGE-A4 antigen above the 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 into either Cohort 1 or Cohort 2. Enrolled subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the ADP-A2M4 cell Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation. Subjects who have enrolled into a Cohort may not enroll into the other Cohort subsequently. Prior to the administration of lymphodepleting chemotherapy all eligibility criteria will be reconfirmed and baseline tumor assessment obtained. Anticancer therapy may be administered between screening and leukapheresis and between leukapheresis and the start of lymphodepletion (bridging therapy), if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods must be adhered to. When the ADP-A2M4 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5) followed by infusion of ADP-A2M4 cells on Day 1. Subjects will remain hospitalized for observation for at least 10 days post T cell infusion.

	An independent Data Safety Monitoring Board (DSMB) will review the ongoing safety during the interventional phase of the study for Cohort 1. Cohort 2 will begin once all subjects have been dosed in Cohort 1. Subjects in both cohorts will have the following study visits for assessment of eligibility, efficacy, safety, health related-outcome and biomarkers: Pre-Screening, Screening, Leukapheresis, Baseline, Lymphodepleting Chemotherapy (Day -7 to Day -4), T cell infusion (Day 1) and immediate post infusion monitoring (Day 1 through Day 8), weekly visits until Week 4 post infusion, then 6, 8, 12, 16 and 24 weeks then every 2 months until disease progression. Subjects will undergo disease monitoring by magnetic resonance imaging (MRI) or computerized tomography (CT) scan at Screening, Baseline, Week 4, Week 8, Week 12, Week 16 and Week 24, and every 2 months 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 6-15. The timepoint at which the subject switches will be driven by the timepoint at which the subject progresses e.g. 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 Primary Efficacy Analysis will be for Cohort 1 only. Clinical cut-off for the primary analysis will occur once the forty-fifth subject dosed in Cohort 1 has up to 6 months follow-up post T cell infusion. At this time, all safety and secondary efficacy endpoints for Cohort 1 only will also be summarized to provide supportive evidence to the primary assessment.
Study Duration	Enrollment is expected to continue for approximately 12 months for Cohort 1 and for an additional 12 months for Cohort 2. The study will be considered complete once all enrolled subjects complete 15 years of follow-up or discontinue the study for any reason.
Study Center(s)	The study will be conducted in approximately 24 sites in North America and Europe. Additional sites may be added at the discretion of the Sponsor.
Number of subjects	Ninety (90) subjects: Forty-five (45) synovial sarcoma and MRCLS subjects in Cohort 1; Forty-five (45) synovial sarcoma subjects in Cohort 2.

Objectives	Endpoints
Primary	
To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	Overall Response Rate (ORR) per RECIST v1.1 by independent review in Cohort 1.
Secondary	
To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	For Cohort 1 and across Cohorts (overall): • 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-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review across Cohorts (overall) For Cohort 1 and across Cohorts (overall): • Time to Response (TTR) • Duration of Response (DoR) • Best Overall Response (BOR) • Progression Free Survival (PFS) • Overall Survival (OS)
Development and validation of an in vitro diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Across Cohorts: • Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay

Characterize the in vivo cellular pharmacokinetics (PK) profile of ADP-A2M4 cells	For Cohort 1 and across Cohorts (overall): • Peak persistence and other relevant PK parameters of ADP-A2M4 cells
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Inclusion Criteria	1. Subject (or legally authorized representative) voluntarily agrees to participate by giving written Informed Consent (and Assent as applicable) in accordance with ICH GCP guidelines and applicable local regulations. 2. Subject (or legally authorized representative) agrees to abide by all protocol required procedures including study related assessments and management by the treating institution for the duration of the study, including long term follow-up. 3. Age ≥16 and ≤75 years at the time the Pre-screening informed consent/assent is signed (Cohort 1). Age ≥10 and ≤75 years at the time the

	Pre-screening informed consent/assent is signed and actual body weight ≥ 40 KG (Cohort 2) 4. Diagnosis of advanced (metastatic or inoperable) synovial sarcoma or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1 only) confirmed by cytogenetics. Inoperable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise. a. For Synovial Sarcoma (Cohort 1 and Cohort 2): confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)). b. For MRCLS (Cohort 1 only): confirmation by the presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) or t(12; 22) (q13;q12). 5. Must have previously received either an anthracycline or ifosfamide containing regimen. 1st-line metastatic treatment with ADP-A2M4 is permissible if ifosfamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumor setting and has progressed within 6 months of receiving treatment. (Subjects who are intolerant of both anthracycline and ifosfamide must have previously received at least one other type of systemic therapy). 6. Measurable disease according to RECIST v1.1. 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. 8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥2+ staining in ≥30% of the cells by immunohistochemistry. 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 or for subjects aged 10 to < 16 years of age, Lansky Score ≥80 %. 10. Left ventricular ejection fraction (LVEF) ≥50%. 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 an 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 a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide). 13. Must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support)[1] within 7 days prior to lymphodepletion and leukapheresis
Platelets	≥ 100 x10^9/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to lymphodepletion and leukapheresis)
Coagulation	
Prothrombin Time (PT) or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation
Renal	

	Glomerular filtration rate (calculated CrCl using only the Cockcroft-Gault equation, or measured using either a 24-hour urine creatinine collection or a radionuclide EDTA test)[2]	≥ 60 mL/min
	Hepatic	
	Serum total bilirubin	≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)
	Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT)	≤ 2.5x ULN
	1. ≥1 x10^9/L (without G-CSF support) in 10 – 15 year olds 2. 24-hour urine creatine clearance or radionuclide EDTA tests should be used to measure the GFR in all subjects: ≥ 65 years old; clinically obese (≥ 30KG/m2) or underweight (≤18.5KG/m2); borderline low calculated CrCl (Cockcroft-Gault) at approximately 60mls/min. Renal function will be reassessed at Baseline using the same methodology.	
Exclusion Criteria	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 (TKI) (e.g. pazopanib)	1 week	1 week
		Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors,)	4 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	Subjects who have received a gene therapy using any DNA-integrating vector other than a lentivirus (retrovirus, AAV, etc.) are excluded from this study. Subjects who have received a gene therapy using a	Not permitted after leukapheresis and prior to lymphodepletion.

			lentiviral vector may be eligible if they have persistence results below the lower limit of quantification (LLOQ) for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.	
		Corticosteroids or any other immunosuppressive therapy. NOTE: Use of topical steroids is not an exclusion. See Section 6.5.1 for exceptions.	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 washout period for palliative radiation to non-target organs).
	Major surgery	N/A	4 weeks. Subjects must have recovered from any surgical related toxicities.
	NOTE: Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician		

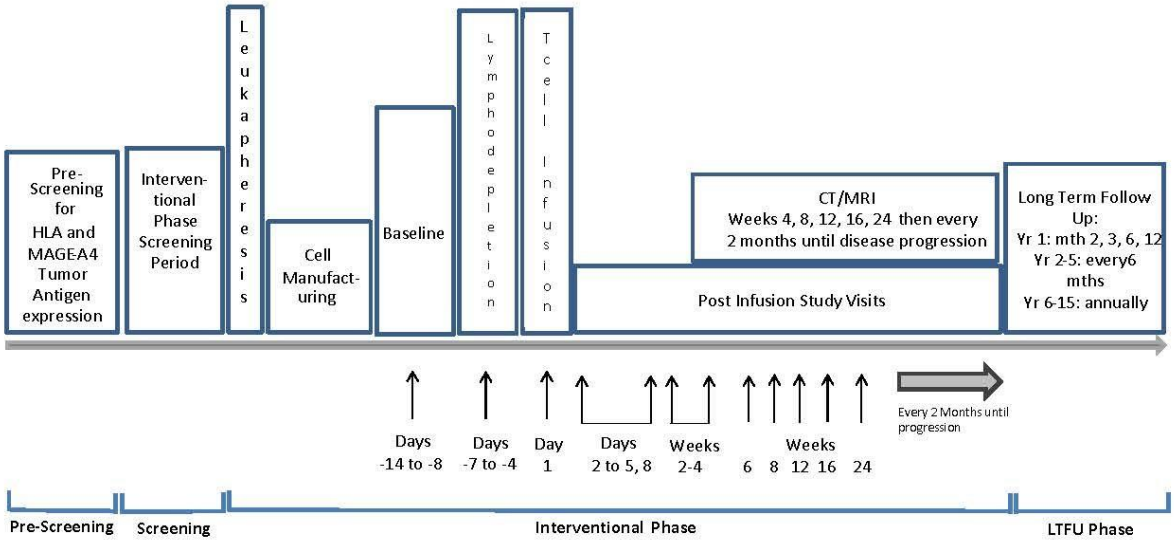
3. Toxicity from previous anti-cancer therapy must have recovered to ≤ Grade 1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g. peripheral neuropathy) can be enrolled.
4. History 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. Symptomatic CNS metastases including leptomeningeal disease. Subjects with a prior history of symptomatic CNS metastasis including leptomeningeal disease must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiation (WBRT) and/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. 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; • Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4; • Uncontrolled clinically significant arrhythmia; • Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months; • Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent); • Congenital or family history of long QT syndrome; • Current uncontrolled hypertension despite optimal medical therapy; • History of stroke or central nervous system bleeding; transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) in last 6 months; • Incipient compression/occlusion of a vital structure (e.g. bronchus; superior vena cava; renal outflow tract) which cannot undergo prophylactic stenting; • COVID-19 infection or a positive COVID-19 RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy. If a subject has a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart. 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 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.
Investigational Product, Dose, Route, Regimen	ADP-A2M4 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 primary clinical endpoint for efficacy is Overall Response Rate (ORR) defined as the proportion of subjects with a complete response (CR) or partial response (PR) via independently reviewed RECIST v1.1 relative to the total number of subjects in the analysis population in Cohort 1. The primary analysis population for safety and efficacy will be the modified intent to treat population (mITT) defined as all subjects who received the ADP-A2M4 cell infusion in Cohort 1. (Null Hypothesis) H_0: $p \leq p_0$, vs. (Alternate Hypothesis) H_1: $p > p_0$, where p_0 (historical control rate) = 0.18. Statistical assumptions include: • The type I error (α) will be no more than 0.025 • The type II error (β) will not exceed 0.1 • Exact Binomial methods will be used to test the hypothesis • The assumed ORR for ADP-A2M4 is 0.40

	Based on the statistical design assumptions above and the hypotheses and clinical assumptions detailed in Section 9, the estimated sample size for the trial is 45 subjects in Cohort 1 for the primary analysis. An additional 45 subjects are to be enrolled in Cohort 2, although no formal hypothesis testing is planned for Cohort 2 or overall (across cohorts). The primary endpoint, ORR per RECIST v1.1 by independent review for Cohort 1, will be evaluated using a one-sided exact-based Clopper-Pearson 97.5% confidence interval (CI). If the lower bound of the 97.5% CI exceeds 18%, the trial has met the pre-specified threshold for demonstrating efficacy. The key secondary efficacy endpoints ORR per RECIST v1.1 by independent review across Cohorts (overall), TTR, DoR, 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. Two-sided 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, PK profile, 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. Efficacy and safety summaries will be displayed across tumor types (overall) and by tumor type. Efficacy and safety summaries will be displayed across cohorts (overall) and by a cohort as indicated above. 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
Cell Manufact-uring
Baseline
Lymphodepletion
T cell Infusion
CT/MRI
Weeks 4, 8, 12, 16, 24 then every 2 months until disease progression
Post Infusion Study Visits
Long Term Follow Up:
Yr 1: mth 2, 3, 6, 12
Yr 2-5: every6 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 24
Weeks
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

Table 1: T&E for Pre-Screening and Interventional Phase

Written Informed Consent must be obtained prior to performing any protocol procedures. A Pre-screening 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.

			Interventional Phase																								
	Pre-Screening	**Screening[1]**	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**															**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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																								Section 8.1.1
Inclusion/Exclusion	X	X		X																					Section 5
Disease History	X	X																							Section 8.1.2
HLA typing	X[12]																								Section 8.2.1

			Interventional Phase																							
	Pre-Screening	**Screening**[1]	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
MAGE-A4 Expression	X																								Section 8.2.2
Cytogenetics testing for translocations		X[1]																							Section 8.2.3
Safety and Efficacy Assessments																									
Medical History		X																							Section 8.4.1
Physical Exam		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	Section 8.4.4
ECOG/Lansky[15]		X		X										X	X	X	X	X	X	X	X	X	X	X	Section 8.4.5

			Interventional Phase																						
	Pre-Screening	**Screening**[1]	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**													**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Height				X																					Section 8.4.8
Weight		X		X													X		X	X	X	X		X	Section 8.4.8
Vital Signs		X		X					X[2]	X	X	X	X	X	X									X	Section 8.4.7
ECG		X		X					X[3]				X												Section 8.4.9.1
Echo/MUGA		X																							Section 8.4.9.2
CT / MRI		X		X													X[14]		X[14]	X[14]	X[14]	X	X	X	Section 8.3.1
Brain MRI				X[4]																					Section 8.4.10
ICE[18]									X	X	X	X	X	X											Section 8.4.19
CAPD[18] (Cohort 2 only)									X	X	X	X	X	X											Section 8.4.20
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**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Hematology		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.12
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																							Section 8.4.18
CMV PCR				X[5]					X[5]						X[5]		X[5]	X[5]	X[5]						Section 8.4.19
Thyroid Function Tests				X																					Section 8.4.15
C-reactive Protein[6]				X					X			X		X	X		X								Section 8.4.21
Ferritin[6]				X					X			X		X	X		X								Section 8.4.22

			Interventional Phase																						
	Pre-Screening	**Screening**[1]	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
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
Persistence (Vector Copies)	X[10]	X[10]		X						X		X		X	X		X		X	X		X	X		Section 8.4.23 LTFU Table 2
RCL (VSV-G DNA)				X																X		X	LTFU Table 2		Section 8.4.24 LTFU Table 2

			Interventional Phase																						
	Pre-Screening	**Screening**[1]	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Leukapheresis, Lymphodepleting Chemotherapy and Investigational Product Administration																									
Leukapheresis			X																						Section 6.1
Fludarabine[11]					X[11]	X[11]	X[11]	X[11]																	Section 6.2
Cyclophosphamide					X	X	X																		Section 6.2
ADP-A2M4 Infusion									X																Section 6.3
Biomarker Assessments[16]																									
Tumor Biopsy				X													X[7]							X	Section 8.6.1
Cytokine and Soluble Protein Analyses[6]				X					X[8]	X		X		X	X		X[7]		X	X		X	X		Section 8.6.2
Liquid Biopsy (Blood Plasma)				X					X[3]								X		-					X	Section 8.6.3

			Interventional Phase																						
	Pre-Screening	**Screening**[1]	**Leukapheresis**	**Baseline**	**Lymphodepleting Chemotherapy**				**T-cell Infusion**	**Post-infusion Assessments**														**Every 2 Months**	**Study Discontinuation**	**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 (days)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	±1					± 3		±3	±3	±7				±28	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**			
Cell Phenotyping and Functional Assays				X					X					X	X		X		X	X		X	X	X	Section 8.6.4
Patient Reported Outcomes																									
EQ-5D-3L				X															X		X	X	See footnote[9]		Section 8.8.1
EORTC-QLQ-C30 (Cohort 2 only)				X															X		X	X	See footnote[13]		Section 8.8.2
PedsQL™ (Cohort 2 only)				X															X		X	X	See footnote[17]		Section 8.8.3

[1] Screening Visit 2 assessments should be completed within 28 days of leukapheresis; CT/ MRI scans and ECHO/MUGA scans, performed as standard of care within 4 weeks prior to Screening Visit 2 (prior to study consent) are acceptable. Cytogentic confirmation of diagnosis can be historic, done as standard of care or be done any time after signing Treatment Consent and does not need to be within 28 day screening window.

[2] Measured pre-infusion, and at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started

[3] Pre-infusion

[4] Within 4 weeks of lymphodepletion

[5] If CMV seropositive at screening, CMV-PCR done at baseline. All CMV seropositive subjects will continue to be monitored by CMV PCR at day 1, week, 2, 4, 6, 8

[6] 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

[7] Can be taken anytime between Week 3 and Week 8

[8] Day 1 samples taken pre-infusion and 2-4 hr. post-start of infusion

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

[10] Only for a subject who has previously received a gene therapy using a lentiviral vector. Subject's must have results below the LLOQ for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.

[11] Fludarabine dose must be adjusted for renal impairment using the Cockcroft-Gault equation/methods described in Section 6.2.1

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

[13] EORTC-QLQ-C30 is for Cohort 2 subjects only; EORTC-QLQ-C30 will also be done at Month 12 if the subject remains in the interventional phase of the study

[14] On study scans from Week 4 through Week 16 should be at least 28 days apart to ensure compliance with RECIST 1.1 requirement for confirmatory scans in the event that an objective response is noted by central read

[15] ECOG should be used in subjects ≥16 years old and Lansky in subjects < 16 years old

[16] Biomarker research Blood draws (cytokine, liquid biopsy and cell phenotyping) will not be collected in pediatric subjects to comply with European recommendations. Blood draws will not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time In the event that blood draws are limited due to these restrictions, blood samples for research will be performed in order of priority as defined in the laboratory Manual

[17] Peds-QL is for Cohort 2 and will be used in subject's 10 - 17 years old

[18] CAPD is for Cohort 2 and will be used in subjects <12 years old. ICE will be used in all subjects ≥ 12 years old

1.3.2. Long Term Follow Up Phase Time & Events Table

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

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 Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.2
Mutagenic agents, other investigational agents or anti-cancer therapies	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	Sections 8.4.24

2. INTRODUCTION

2.1. Study Rationale

2.1.1. Rationale for using MAGE-A4 TCR in synovial sarcoma and myxoid/round cell liposarcoma

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

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

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

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-A2M4 are autologous CD4 and CD8 positive T cells that have been transduced with a self-inactivating lentiviral vector expressing a high affinity MAGE-A4 specific T cell receptor (TCR). MAGE-A4 is a cancer/testis antigen (CTA) that has restricted expression in normal tissue, and is expressed across a range of solid tumors at varying frequencies.

ADP-A2M4 recognizes the MAGE-A4230-239; GVYDGREHTV peptide derived from the MAGE-A4 family of CTAs. Thus, ADP-A2M4 incorporates an affinity enhanced TCR capable of recognizing the human leukocyte antigen (HLA)-A*02-GVYDGREHTV antigen complex.

The safety of ADP-A2M4 has been shown in subjects with different tumor types in an ongoing Phase 1 study (NCT03132922). Data of another genetically engineered T cell investigational product, NY-ESO^{c259}T, in synovial sarcoma provides evidence that TCR therapies can be effective in solid tumors [D'Angelo, 2018a].

2.2. Background

2.2.1. MAGE-A4 background

The cancer/testis antigens (CTA) comprise a number of genes that have restricted expression to the testis, but have been identified by their expression in various tumor types [Caballero, 2009]. These include NY-ESO-1, MAGE-A family, SSX2, BAGE, GAGE, and CT7 among others.

Most of these testis-specific genes are coded on the X chromosome. Several of these antigens, including MAGE-A3, MAGE-A10 and MAGE-A8, also have expression in placenta [Caballero, 2009]. In general, melanoma, ovarian cancer and lung cancer, particularly of the squamous cell type, have the highest frequency of RNA expression across the CTAs. Epithelial cancers such as breast, bladder and prostate cancer have intermediate expression, with frequency of mRNA expression in the range of 30% to 50%. CTAs often have coordinated expression, with several expressed in a single tumor [Gure, 2005]. In addition to RNA, immunohistochemistry is often used to determine the expression levels of CTAs. While it is generally seen that mRNA expression of these antigens correlates well with protein expression it should be noted that there is frequently heterogeneous expression of protein across the tumor, with strong expression in a small subset of tumor cells. There is also epigenetic and post-transcriptional modification that determines protein expression levels under certain conditions.

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

MAGE-A4 has been described as having high expression in synovial sarcoma and MRCLS. A recent study showed that 82% of synovial sarcoma samples expressed MAGE-A4 when evaluated by Immunohistochemistry (IHC) and high expression of NY-ESO-1 and MAGE-A4 was significantly correlated with the presence of necrosis and advanced clinical stage [Iura, 2017a]. [redacted]. A further report suggested that 67.7% of MRCLS samples, express MAGE-A4 [Iura, 2017b]. [redacted]

2.2.2. Discovery of ADP-A2M4

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

The Investigational Product (IP) is comprised of autologous CD4 and CD8 T cells obtained from eligible subjects who have MAGE-A4 expressing tumors and who are HLA-A*02 positive. Subjects who are HLA-A*02:05 are excluded because alloreactivity has been observed in vitro with ADP-A2M4 to this HLA allele. The T cells undergo self-inactivating (SIN) lentiviral transduction with ADP-A2M4 specific nucleic acid under Good Manufacturing Practice (GMP) conditions. The resulting polyclonal ADP-A2M4 specific peptide enhanced affinity receptor (SPEAR™) T cells are now genetically engineered to target the antigen on the subject's MAGE-A4 positive advanced tumor.

2.2.3. Current Therapeutic Options for Synovial Sarcoma & MRCLS

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

Synovial Sarcoma

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

Surgery is the standard therapy for localized disease. Patients with advanced synovial sarcoma receive ifosfamide and/or doxorubicin, as the first-line of therapy [ESMO, 2014].

Doxorubicin-based first-line metastatic doublet therapies, such as doxorubicin in combination with the anti-PDGFR alpha monoclonal antibody olaratumab [Lilly, 2019], have not demonstrated improved clinical benefit compared to single-agent doxorubicin.

There is no specific standard of care (SoC) in second line therapies and beyond. Pazopanib is approved in the U.S and in Europe for patients with synovial sarcoma previously treated with chemotherapy [Votrient™ US Prescribing Information, EU SmPC]. A randomized double blind placebo controlled Phase 3 trial of pazopanib was conducted in patients with advanced STS. Overall response rate (ORR) as assessed by Data Safety Monitoring Board (DSMB) for the intent to treat (ITT) population was 4%, median duration of response (DoR) of 9 months, and median progression free survival (PFS) of 4.6 months compared with 1.6 months for placebo (HR=0.35, p<0.001). Median overall survival (OS) was 12.6 months compared with 10.7 months for placebo (HR=0.87; 95% CI: 0.67, 1.12). Only 38 subjects with synovial sarcoma (randomized 2:1) were included in the study with a median PFS of 4.1 months in the pazopanib arm vs 0.9 months for placebo (HR= 0.43; 95% CI 0.19, 0.98). The response rate is not reported by histology [Votrient™ US Prescribing Information, EU SmPC]. In a Phase 2 non-randomized study of pazopanib (EORTC Study 62043), responses as assessed by the Investigator were reported in 5/37 (13%) subjects with synovial sarcoma [Sleijfer, 2009].

The response rate in a retrospective analysis of gemcitabine and docetaxel in patients with synovial sarcoma was 10% [Abouharb, 2014]. Several other agents have shown no appreciable anti-tumor activity in synovial sarcoma; these include many novel classes of agents such as HDAC-inhibitors [Cassier, 2013], IGF-1R antibodies [Pappo, 2014; Olmos, 2010], mTOR inhibitors [Schwartz, 2013], vascular disrupting agents [Blay, 2015] and anti-CTLA4 antibodies [Maki, 2013].

Pediatric Synovial Sarcoma is the most common primary Non-rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS) in children accounting for up to 50% of NRSTS [Sultan 2009]. Treatment paradigms for the management of paediatric SS is similar to adult patients and involves the use of multimodality treatment (i.e. surgery, radiotherapy and chemotherapy) for high-risk primary tumors, and the use of anthracycline-containing chemotherapy for first-line metastatic disease management with off-label use of pazopanib as a second-line therapy. The prognoses of primary synovial sarcoma in children is better than in adult patients probably because children, especially those less than 10 years old, have better tumor biology and lower genetic instability as manifest by smaller, ≤ 5cm, primary tumors in this patient subpopulation [Gootee, 2019]; in this context, probability of metastatic disease post first-line primary tumor treatment seems to increase with age (i.e. prognosis: children less than 10 years old > older adolescents > adults) [Younger, 2020]. To date, there are no published patient series' annotating the natural history and prognosis of children with metastatic synovial sarcoma probably because metastatic disease is very rare given the biological differences between pediatric and adult sarcomas, and since the majority of children who do relapse after primary sarcoma treatment do so with mainly local/locoregional disease which in most cases continues to be therapeutically sensitive to chemotherapy and/or radiotherapy [Soole, 2014]. Overall, the potential therapeutic opportunity for ADP-A2M4 cells is in children with locoregional or metastatic synovial sarcoma which has become refractory to alkylating agent chemotherapy.

2.2.4. Emerging Data for ADP-A2M4 SPEAR T-cells in Synovial Sarcoma

Therapeutically effective treatment options for patients with advanced/metastatic synovial sarcoma are limited. The median survival upon relapse from first-line therapy is approximately 12 months [Minchom, 2010] and the ORR from prospective trials for existing therapies, such as alkylating agent chemotherapy and pazopanib are ≤ 13%.

Thirty-eight adult subjects with a variety of different solid tumors including 16 subjects with metastatic synovial sarcoma have received treatment with a single dose of ADP-A2M4 up to 9.9756 x 10^9 transduced cells within the phase 1 ADP-0044-001 study. Synovial sarcoma subjects represented the most frequent tumor type in the phase 1 study, and the majority of the subjects treated in Group 3/Expansion cohort. Of the 16 subjects with synovial sarcoma, most subjects were males (62.5%), most subjects were White (87.5%) and the median age was was 49.0 years (range 31 to 76 years). The median ADP-A2M4 dose in synovial sarcoma was 9.28 x 10^9 transduced cells (range: 3.4 to 10 x 10^9). The reported adverse events are consistent with those typically experienced by patients with advanced cancer undergoing cytotoxic chemotherapy or cancer immunotherapy (e.g, cytopenias, fatigue, CRS). The most common AE ≥ Grade 3 occurring in ≥ 25% of subjects with synovial sarcoma were, lymphopenia/lymphocyte count decreased (93.3%), leukopenia/WBC count decreased (100%), neutropenia/neutrophil count decreased (88.0%), neutropenia/neutrophil count decreased(81%), anemia/RBC decreased (44%), thrombocytopenia/platelet count decreased (44.0%), hypophosphatemia (44%), rash (19%), CRS (13%), decreased appetite (6%) and hypotension (6%). Cytokine release syndrome (any Grade) was reported in 88% of the subjects with synovial sarcoma. There was one (1) Grade 5 SAE of prolonged pancytopenia with hypoplastic bone marrow considered possibly related to ADP-A2M4. In subjects with synovial sarcoma, the ORR (confirmed responses) was 44% (95%CI: 16.34, 67.71). The Best Overall Response was PR (7), SD (8), PD (1). Disease control rate was 94% with 11 patients still alive at time of 1-September-2020 data cut-off. Subject responses were durable with a median duration of response of 28 weeks range: 12-72 weeks [CTOS, 2020]. This data supports the continued evaluation of ADP-A2M4 in advanced/metastatic synovial sarcoma.

Myxoid/Round Cell Liposarcoma (MRCLS)

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

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

pace of progression. A variety of therapies are used in the second-line setting and beyond although only trabectedin and eribulin are approved. A randomized open label phase 2 study of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma enrolled 270 patients. Patients were randomized to receive either a 24 hour infusion of 1.5 mg/m^2 of trabectedin once every 3 weeks, or a 3 hour infusion of 0.58 mg/m^2 of trabectedin once every week for three weeks of a 4 week cycle. The treatment regimen that was determined to be most beneficial was the 24 hour infusion of 1.5mg/m^2 of trabectedin once every 3 weeks. One hundred and thirty six patients were randomized to this arm of the study and the ORR was 5.6% [Demetri, 2016].

A subsequent randomized, phase 3, open-label, active-controlled trial comparing trabectedin (n=345) treatment with dacarbazine (n=173) in patients with unresectable, locally advanced or metastatic leiomyosarcoma (73%) or liposarcoma (27%) (dedifferentiated, myxoid round cell, or pleomorphic) and previous treatment with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen demonstrated an overall response rate (ORR of 9.9% (CI 0.72, 3.2) with trabectedin, an improvement of median progression-free survival (PFS) of 5.6 vs 1.5 months on dacarbazine but no difference in overall survival [Demetri, 2016]. Eribulin demonstrated an improvement in survival (median OS 13.5 vs 11.5 months; HR= 0.768; 95% CI, 0.618; 0.954) compared with darcarbazine in subjects with liposarcoma and leiomyosarcoma who received 2 or more prior lines of therapy. There was no difference in PFS and ORR was 3.9% with Eribulin and 4.9% with darcarbazine in all patients enrolled. In patients with liposarcoma the response rate was 1.4% [Schöffski, 2016]. Despite the approval of these two agents, overall survival in patients with relapsed disease remains 12-13 months [Demetri, 2016; Schöffski, 2016] and the ORR from prospective trials for existing therapies is < 10%.

A TCR T-cell product targeted against the NY-ESO-1 cancer testis antigen has shown potentially promising clinical activity in eight MRCLS subjects [D'Angelo, 2018b]. For MAGE-A4, in Study ADP-0044-001, two MRCLS subjects were dosed with ADP-A2M4 cells. At the time of Data cut-off, 1 Sept 2020, no MRCLS subjects had responded to ADP-A2M4. ADP-A2M4 was however safe and well tolerated in MRCLS subjects in this phase 1 trial.

2.3. Benefit: Risk Assessment

The results of clinical and non-Clinical studies conducted with ADP-A2M4 cells are summarized in the ADP-A2M4 Investigator's Brochure. This section outlines the potential benefits, risks and the overall benefit: risk for this study.

2.3.1. Benefit

Although the basis for including both synovial sarcoma and MRCLS subjects in Cohort 1 of this study was the reported a high frequency of MAGE-A4 expression in both synovial sarcoma and myxoid liposarcoma [Iura, 2017a; Iura, 2017b], as well as the historical clinical activity of the NY-ESO-1 TCR in both synovial sarcoma and MRCLS, Preliminary evaluation of MRCLS response and MAGE-A4 antigen status in both the ADP-0044-001 and Cohort 1 ADP-0044-002 studies would suggest that ADP-A2M4 is not as clinically active in MRCLS as it is in synovial

sarcoma. This is possibly because of a comparatively lower MAGE-A4 antigen score distribution.

For these reasons, Cohort 2 will only enroll adult and pediatric (10-17 years old) subjects with synovial sarcoma as such patients are likely to derive the greatest therapeutic benefit from the ADP-A2M4 cell product especially since study ADP-0044-001 has shown an ORR of 44% in sixteen heavily pre-treated metastatic synovial sarcoma adult subjects who had a median of three prior lines of treatment [CTOS, 2020]. The therapeutic benefit from ADP-A2M4 SPEAR T-cells in children with advanced/metastatic synovial sarcoma is anticipated to be similar to adult patients as long as the MAGE-A4 expression distribution and endogenous qualitative function of T-cells in pediatric patients are similar to adults.

The data from study ADP-0044-001 in combination with emerging efficacy findings for synovial sarcoma subject in Cohort 1 of study ADP-0044-002 would indicate that ADP-A2M4 is a promising cell product in metastatic synovial sarcoma especially since there is no specific standard of care beyond first-line ifosfamide and/or doxorubicin for patients with advanced (inoperable)/metastatic synovial sarcoma.

2.3.2. Risk

The safety and tolerability of ADP-A2M4 is being assessed in Phase 1 trial (study ADP-0044-001) across multiple tumor types and in the ongoing Cohort 1 of study ADP-0044-002 including synovial sarcoma and MRCLS. Toxicities observed with ADP-A2M4 are common to other TCR or CAR-T therapies or standard of care chemotherapies.

Toxicities such as CRS, ICANS and pancytopenia/aplastic anemia are specific to TCR and CAR-T therapies and therefore guidelines for management of these events are included in Section 10.5. An advantage of TCR therapy is that they are generally administered once, and the vast majority of toxicities resolve within 4 to 6 weeks after T cell infusion.

Alloreactivity, whereby TCRs reactive towards a given peptide-MHC complex display cross-reactivity towards different HLA allelic variants, is a theoretical risk. Pre-clinical data indicate strong anti-HLA-A*02:05 alloreactivity, making A*02:05 an exclusion allele. Data also indicate decreased potency against MAGE-A4230-239 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-A2M4 and 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: 1) extensive preclinical evaluation of the ADP-A2M4 which has incorporated learnings from other adoptive T cell therapy programs [ADP-A2M4 Investigator 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 cytokine release syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and pancytopenia/aplastic anemia as well as preventive measures for infectious complications, and 6) a Data Safety Monitoring Board (DSMB) to evaluate safety during the course of Cohort 1.

The potential risks for Cohort 2 (synovial sarcoma only) in both adult and pediatric subjects (10-17 years old) are expected to be similar to the emerging safety profile in Cohort 1 of study ADP-0044-002, as well as similar to the safety profile reported in the sixteen synovial sarcoma subjects previously dosed in the phase 1 trial, study ADP-0044-001 [CTOS, 2020]. Moreover, when combined with the emerging safety profile in Cohort 1, the additional 45 synovial sarcoma subjects in Cohort 2 will permit a deeper understanding and a better estimate of the frequency of adverse events of special interest (AESI) across a broad age range of patients i.e. incidence of CRS, ICANS and pancytopenia in synovial sarcoma subjects treated with ADP-A2M4 cells compared to safety data from Cohort 1 alone.

2.3.3. Overall benefit: risk conclusion

In Cohort 1, based on the initially promising emerging efficacy and safety findings from the Phase 1 ADP-A2M4 SPEAR™ T-cell trial (study ADP-0044-001), it was justifiable from a benefit-risk perspective to treat subjects with both advanced synovial sarcoma and MRCLS as they each constituted patient populations with a high unmet medical need, albeit with distinctly different metastatic disease natural histories. However, as more mature data has accrued from study ADP-0044-001 in combination with emerging findings from Cohort 1 of this ongoing Phase 2 trial (see Section 4.2, below), it has become apparent that ADP-A2M4 cells may potentially be less clinically active in MRCLS compared to synovial sarcoma. Therefore, at this time, continued evaluation of ADP-A2M4 treatment in Cohort 2 is only justifiable for synovial sarcoma subjects from a therapeutic benefit perspective. In regard to mitigation of risks, in both adults and children (10-17 years old), measures to ensure safe administration of ADP-A2M4 have been included in this study protocol, with close monitoring for toxicities and guidelines for their management.

The potential risks identified in association with ADP-A2M4 are justified by the anticipated benefits which may be afforded to both adult and pediatric/adolescent patients with advanced (inoperable)/metastatic synovial sarcoma in Cohort 2. Indeed, real-world evidence in metastatic synovial sarcoma suggests that pazopanib - which is approved for 2nd-line metastatic soft tissue sarcoma treatment in the United States and Europe - is not the most frequently administered 2nd-line therapy at several major synovial sarcoma centres in the United States possibly because of its low ORR [Pollack, 2020]. Since the outcome of both adults and children with advanced (inoperable)/metastatic synovial sarcoma is poor, this study provides a unique therapeutic opportunity for ADP-A2M4 to potentially become the first licensed cell therapy product in post-1st-line advanced (inoperable)/metastatic synovial sarcoma, if the overall benefit-risk findings from this phase 2 trial (study ADP-0044-002) are favorable.

3. OBJECTIVES AND ENDPOINTS

Objectives	End Points
Primary:	
To evaluate the efficacy of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review in Cohort 1
Secondary:	
To evaluate the safety and tolerability of autologous genetically modified T cells (ADP-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	For Cohort 1 and across Cohorts (overall): • 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-A2M4) in HLA-A*02 positive subjects with MAGE-A4 expressing advanced synovial sarcoma or MRCLS	• Overall Response Rate (ORR) per RECIST v1.1 by independent review across Cohorts (overall) For Cohort 1 and across Cohorts (overall): • Time to Response (TTR) • Duration of Response (DoR) • Best Overall Response (BOR) • Progression Free Survival (PFS) • Overall Survival (OS)

Development and validation of an in vitro diagnostic (IVD) assay for the screening of tumor antigen expression for regulatory approval	Across Cohorts: • Retention of additional tumor tissue during Pre-screening to enable development and validation of the MAGE-A4 antigen expression companion diagnostic assay
Characterize the in vivo cellular pharmacokinetics (PK) profile of ADP-A2M4 cells	For Cohort 1 and across Cohorts (overall): • Peak persistence and other relevant PK parameters of ADP-A2M4 cells
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2 single arm, open label study of genetically engineered ADP-A2M4 in HLA-A*02 subjects with MAGE-A4 expressing metastatic or inoperable (advanced) synovial sarcoma or myxoid/ myxoid round cell liposarcoma (Cohort 1 only). Only subjects with advanced synovial sarcoma will be eligible for Cohort 2. The study consists of two separate, independent, serially enrolled subject cohorts: Cohort 1 and Cohort 2.

Enrollment into Cohort 1 is expected to continue for approximately 12 months and is close to completion at the time of this amendment. Forty-five subjects have been enrolled and 26 subjects have been treated with ADP-A2M4 to date. Enrollment will continue to ensure that at least 45 subjects are dosed in Cohort 1. Dosing is expected to be complete in Cohort 1 in March 2021. Data from subjects in Cohort 1 only will be used for the primary study endpoint and primary statistical analysis.

The clinical and scientific rational for including Cohort 2 is to provide an expanded safety and efficacy data set overall in both adults and children (10-17 years old) with inoperable (advanced)/metastatic synovial sarcoma to supplement the primary assessment for Cohort 1. Subjects who were previously enrolled in Cohort 1 may not enroll into Cohort 2.

4.1.1. Pre-screening

Subjects will sign a Pre-screening Informed Consent Form (ICF) and undergo initial screening for the relevant HLA 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 consent in accordance with IRB/IEC approved processes and any local requirements in advance of providing subjects with a HLA buccal/ cheek swab test and/ or sending tissue for MAGE-A4 testing.

4.1.2. Screening

Subjects who have pre-screened 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 the study. Screening assessments should be completed within 28 days of leukapheresis; CT/ MRI scans and ECHO/MUGA scans, performed as standard of care within 28 days prior to Screening Visit 2 (i.e. prior to treatment consent) are acceptable. Cytogenetic confirmation of diagnosis can be historic, done as standard of care, or be done any time after signing Treatment Consent and does not need to be within 28 day screening window.

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-A2M4 cell Investigational Product (IP). Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation.

Anticancer therapy may be administered between screening and leukapheresis, and between leukapheresis and the start of lymphodepletion (bridging therapy), if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods must be adhered to (see Section 5.3). Subjects must be ready to receive IP as the next treatment once manufacturing and any mandatory washout periods are complete even if they remain stable on bridging therapy, provided they have measurable disease per RECIST v1.1.

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

Once the ADP-A2M4 cells are available at site, subjects will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5) (Section 6.2) followed by infusion of ADP-A2M4 cells on Day 1 (Section 6.3). The lymphodepleting chemotherapy may be given as an outpatient treatment or subjects may be hospitalized at the discretion of the Investigator. The T cell infusion will be given as an inpatient procedure. Subjects will remain hospitalized for observation for at least 10 days post T cell infusion. 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.

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 local and independent review 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’), disease progression will not be determined before 4 weeks (28 days) post infusion of ADP-A2M4 unless there is unequivocal clinical evidence of deterioration. Therefore, imaging scans should not be performed earlier than 4 weeks (on or after 28 days) post infusion.

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 adverse events in accordance Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements for gene therapy clinical trials [FDA, 2006a; FDA, 2010; EMA, 2009].

Subjects will be seen in the clinic for evaluation according to Main T&E Table 1 (Section 1.3.1) until disease progression. Thereafter, subjects will undergo assessments/procedures according to the LTFU T&E Table 2 (Section 1.3.2). The timepoint at which the subject switches to the LTFU assessments/procedures will be driven by the timepoint at which the subject progresses e.g. if there is disease progression at Week 12, the next visit would be due at Week 24 (Month 6).

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

4.2. Scientific Rationale for Study Design

This is a Phase 2 single arm, open-label study with ADP-A2M4 cells for the treatment of subjects with advanced synovial sarcoma or MRCLS who are HLA-A*02 positive and have tumors that express MAGE-A4.

MAGE-A4 is a cancer testis antigen that is highly expressed in synovial sarcoma and MRCLS tumors making it an attractive target. Preliminary clinical evidence in Study ADP-0044-001 has shown an ORR (confirmed responses) of 44% (95% CI: 16.34, 67.71) in advanced (inoperable)/metastatic synovial sarcoma with a disease control rate of 94% including 11 out of 16 patients who were still alive at time of 1-September-2020 data cut-off. Synovial sarcoma responses were durable with a median duration of response of 28 weeks (range: 12-72 weeks). [CTOS, 2020]. This ORR is considerably superior than response rates reported with agents currently being used as 2nd line therapies for soft tissue sarcoma (Section 2.2.3).

On this basis, this Phase 2 study (ADP-0044-002) will be a single arm, non-comparative study with a primary efficacy endpoint of Overall Response Rate (ORR) per RECIST v1.1 by independent review in 2 Cohorts where the primary study endpoint will be evaluated in Cohort 1. The historical ORR for first-line metastatic soft-tissue sarcoma patient populations ranges from 4%-13% (Section 2.2.3). To account for the potential variability in historical control response rate, a more conservative historical ORR of 18% has been estimated for therapies administered in the post 1st-line metastatic synovial sarcoma setting, and will be used to evaluate the efficacy of ADP-A2M4 by hypothesis testing (Section 9).

At the time of this Protocol Amendment (05FEB2021) the ADP-0044-002 study has been enrolling subjects for approximately 12 months. Fifty-three adult subjects have been enrolled, and 31 subjects have received treatment with a single dose of ADP-A2M4 in Cohort 1 including 27 adult subjects with advanced (inoperable)/metastatic synovial sarcoma and 4 subjects with MRCLS. [redacted].

The clinical and scientific rationale for including Cohort 2 is to provide an expanded safety and efficacy dataset overall for metastatic or inoperable (advanced) synovial sarcoma, in both adults and children (10-17 years old) to supplement the primary assessment for Cohort 1.

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 of HLA-A*02:01, HLA-A*02:03 or HLA-A*02:06. HLA-A*02 alleles having the same protein sequence as these alleles in the antigen binding domains (P group) will also be included. 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.

Due to the risk of alloreactivity subjects positive for HLA-A*02:05 in either allele are ineligible. Subjects with HLA-A*02 alleles having the same protein sequence as HLA-A*02:05 in the antigen binding domains (P groups) will also be excluded. Other alleles may be exclusionary after consultation with the sponsor. HLA eligibility testing will be done via Adaptimmune designated central laboratory.

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 high proportion of subjects expected to be excluded based on HLA status, an optional buccal swab kit may be offered to subjects during pre-screening 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 associated instructions would be sent to potential subjects who have provided written 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 screening.

4.2.1.2. MAGE-A4 Expression in Tumor

MAGE-A4 expression was reported in synovial sarcoma (82%) and myxoid liposarcoma (68%) cases [Iura, 2017a; Iura, 2017b]. ADP-A2M4 cells have been shown to produce strong IFNγ responses against tumor cell lines (derived from non-small cell lung cancer, prostate carcinoma, melanoma and ovarian carcinoma) expressing high MAGE-A4 mRNA levels (>10,000 MAGE-A4 transcripts). In addition, ADP-A2M4 cells elicited a strong IFNγ response against a primary melanoma tissue material expressing high MAGE-A4 mRNA and protein expression levels. Since no adequate models to define the threshold of ADP-A2M4 cell activation are currently available, this protocol will select for subjects with high MAGE-A4 expression. As such, Adaptimmune will be using a conservative cutoff (≥2+ in ≥ 30% of tumor cells) to ensure sufficient expression of the antigen.

To ensure that the subject's tumor has the potential to be targeted by the ADP-A2M4 cells, the tumor specimen will be screened at a central reference laboratory for the expression of MAGE-A4 by IHC using a Clinical Laboratory Improvement Amendments (CLIA)-validated Clinical Trial Assay.

Optional remote consent to MAGE-A4 testing is permitted for any clinical site that has the necessary written consent processes in place and has obtained the relevant IRB/IEC and local

approvals. This allows subjects with archival specimens available to consent for MAGE-A4 testing without requiring travel to a clinical study site.

4.2.2. T Cell Manufacturing

ADP-A2M4 is autologous CD4 and CD8 T cells engineered with an affinity-enhanced TCR to target the tumor antigen MAGE-A4. Autologous T cells are obtained from eligible subjects who have MAGE-A4 positive tumors and who have appropriate HLA-A. The CD4 and CD8 T cells are transduced with a SIN lentivirus vector expressing the MAGE-A4 (affinity enhanced clone 1032) under GMP conditions. The product of this transduction is polyclonal T cells which are designed to target MAGE-A4 in tissue. The transfer SIN lentiviral vector has been meticulously designed to contain the genetic elements required for function and for maximum biosafety [Dull, 1998]. Many reports provide evidence supporting the relative biosafety of SIN lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the lentivirus long terminal repeat (LTR) in comparison to the γ retroviral vectors [Montini, 2006; Maruggi, 2009; Modlich, 2009; Montini, 2009].

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

4.2.3. Lymphodepletion

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

Evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia and acute leukemia using adoptive cellular therapy including a CAR showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in a previously cyclophosphamide-only preparative regimen [Turtle, 2015]. Cyclophosphamide was administered at 30 – 60 mg/kg x 1 day and fludarabine at 25 mg/m^2/day x 3 – 5 days. Effective lymphodepletion has also been demonstrated in other CAR-T cell studies using reduced cyclophosphamide dosing, together with fludarabine [Batlevi, 2016].

Data from an open label non-randomized multi-cohort pilot study of genetically engineered NY-ESO-1 SPEAR™ T cells in HLA-A2+ patients with synovial sarcoma (NCT01343043) suggests that fludarabine is an important component of T-cell lymphodepleting regimens and fludarabine 30 mg/m^2 given daily for 4 days in combination with cyclophosphamide may be

associated with more objective responses [D'Angelo, 2018] (see Section 2.2.3). The CD19 CAR-T product tisagenlecleucel, also utilizes fludarabine 30 mg/m^2 for 4 days in combination with cyclophosphamide.

The lymphodepleting regimen in this study consists of intravenous fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600 mg/ m^2/day for 3 days (Days -7 to -5).

4.2.4. Long Term Follow-up

Subjects exposed to gene therapies may be at risk for delayed adverse events 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 long term follow up (LTFU) evaluation in the study is designed to adhere to the FDA and EMA guidance for long term follow up of subjects in gene therapy clinical trials [FDA, 2006a; FDA, 2006b; FDA, 2010; EMA, 2009], and involves monitoring subjects who have been exposed to lentivirus-mediated gene transfer in this clinical study for 15 years. Further information on safety monitoring for theoretical risks associated with the use of lentiviral vectors and potential for insertional oncogenesis, as well as safety monitoring are available in Section 10.7, Appendix 7.

4.3. Justification for Dose

The cell dose of ADP-A2M4 is within the range of 1×10^9 to 10×10^9 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 or an additional leukapheresis collection may be 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-A2M4 is being assessed in a Phase 1 trial of multiple tumor types including synovial sarcoma and MRCLS (NCT03132922). Doses up to 9.96 x 10^9 have been well tolerated in this Phase 1 dose escalation study and was associated with a high ORR in 16 advanced (inoperable)/metastatic synovial sarcoma subjects [CTOS, 2020].

Since the pharmacological effect of actual body weight on the biodistribution and pharmacometric profile of ADP-A2M4 SPEAR T-cells has not been established to date in adult patients from Cohort 1, children aged 10-17 years old will only be eligible for dosing in Cohort 2 if their body weight is ≥ 40KG. It is anticipated that the dosing of children < 40KG in the future will only be possibly based on the pediatric dose, exposure and response relationships derived from Cohort 2 either through extrapolation, or utilizing modelling/simulation pharmacometric techniques if very few or no children with advanced/metastatic synovial sarcoma have been dosed in Cohort 2 by the end of study ADP-0044-002.

4.4. End of Study Definition

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

5. STUDY POPULATION

5.1. HLA and Antigen Pre-screening

To be eligible for Pre-screening (Visit 1) subjects must be aged ≥10 and ≤75 years with a diagnosis of advanced (metastatic or inoperable) synovial sarcoma (Cohort1 or Cohort 2) or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1) confirmed by either histology or cytogenetics. Confirmation of diagnosis by cytogenetics is required prior to leukapheresis.

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 all of the following criteria prior to leukapheresis (i.e. at Screening (Visit 2)) AND prior to lymphodepleting chemotherapy (i.e. at Baseline) to be eligible to participate in this study.

1. Subject (or legally authorized representative) voluntarily agrees to participate by giving written informed consent (and Assent as applicable) in accordance with ICH GCP guidelines and applicable local regulations.
2. Subject (or legally authorized representative) agrees to abide by all protocol required procedures including study related assessments, and management by the treating institution for the duration of the study including long term follow-up.
3. Age ≥16 and ≤75 years at the time the Pre-screening informed consent/assent is signed (Cohort 1). Age ≥10 and ≤75 years at the time the Pre-screening Informed Consent/Assent is signed and actual body weight ≥ 40 KG (Cohort 2)
4. Diagnosis of advanced (metastatic or inoperable) synovial sarcoma or myxoid liposarcoma / myxoid round cell liposarcoma (Cohort 1) confirmed cytogenetics. Inoperable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise.
    a. For Synovial Sarcoma (Cohort 1 and Cohort 2): confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)).
    b. For MRCLS (Cohort 1): confirmation by the presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) or t(12; 22) (q13;q12).
5. Must have previously received either an anthracycline or ifosfamide containing regimen. 1st-line metastatic treatment with ADP-A2M4 is permissible if ifosfamide +/- doxorubicin has been administered in either the pre-operative (neoadjuvant) or post-operative (adjuvant) primary tumor setting and has progressed within 6 months of

receiving treatment. (Subjects who are intolerant of both anthracycline and ifosfamide must have previously received at least one other type of systemic therapy).

6. Measurable disease according to RECIST v1.1.
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 as these alleles in the peptide binding domains (P group) will also be included. Other HLA-A*02 alleles may be eligible after adjudication with the sponsor.
8. Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression of ≥2+ staining in ≥30% of the cells by immunohistochemistry. 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 or for subjects aged 10 to < 16 years old, Lansky Score ≥ 80 %.
10. Left ventricular ejection fraction (LVEF) ≥50%.
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 an 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 a FCBP starting at the first dose of chemotherapy and continuing for 4 months thereafter (or longer if indicated in the country specific monograph/label for cyclophosphamide).
13. Must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support)[1] within 7 days prior to lymphodepletion and leukapheresis
Platelets	≥ 100 x10^9/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)

Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to leukapheresis and lymphodepletion)
Coagulation	
Prothrombin Time or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation. Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Renal	
Glomerular filtration rate (calculated CrCl using only the Cockcroft-Gault equation, or measured using either a 24-hour urine creatinine collection or a radionuclide EDTA test) [2]	≥ 60 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 x ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)

Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT)	≤ 2.5x ULN
1. ≥1 x10^9/L (without G-CSF support) in 10 – 15 year olds 2. 24-hour urine creatine clearance or radionuclide EDTA tests should be used to measure the GFR in all subjects: ≥ 65 years old; clinically obese (≥ 30KG/m2) or underweight (≤18.5KG/m2); borderline low calculated CrCl (Cockcroft-Gault) at approximately 60mls/min. (see Section 8.4.11 for further details). **Renal function will be reassessed at baseline using the same methodology.**	

5.3. Exclusion Criteria

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

14. 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.
15. 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 (TKI) (e.g. pazopanib)	1 week	1 week
Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors,)	4 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 week in the absence of tumor response. The subject should be excluded if their disease is responding to an experimental vaccine given within 6 months

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Gene therapy using an integrating vector	Subjects who have received a gene therapy using any DNA-integrating vector other than a lentivirus (retrovirus, AAV, etc.) are excluded from this study. Subjects who have received a gene therapy using a lentiviral vector may be eligible if they have persistence results below the lower limit of quantification (LLOQ) for at least 2 samples taken at least 1 month apart. At least 1 of these tests must be performed by Adaptimmune as part of Pre-screening or Screening.	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 6.5.1 for exceptions.	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 washout period for palliative radiation to non-target organs).

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Major surgery	N/A	4 weeks. A subject must be fully recovered from any surgical related toxicities.
NOTE: Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician		

16. Toxicity from previous anti-cancer therapy must have recovered to ≤ Grade 1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g. peripheral neuropathy) can be enrolled.
17. History of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study.
18. 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.
19. Symptomatic CNS metastases including leptomeningeal disease. Subjects with a prior history of symptomatic CNS metastasis including leptomeningeal disease must have received treatment (i.e., stereotactic radiosurgery (SRS), whole brain radiation (WBRT) and/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.
20. 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.
21. Uncontrolled intercurrent illness including, but not limited to:
    - Ongoing or active infection;
    - Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4;
    - Uncontrolled clinically significant arrhythmia;
    - Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months;

- Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent);
- Congenital or family history of long QT syndrome;
- Current uncontrolled hypertension despite optimal medical therapy;
- History of stroke or central nervous system bleeding; transient ischemic attack (TIA) or reversible ischemic neurologic deficit (RIND) in last 6 months.
- Incipient compression/occlusion of a vital structure (e.g. bronchus; superior vena cava; renal outflow tract) which cannot undergo prophylactic stenting;
- COVID-19 infection or a positive COVID-19 RT-PCR test within 28 days of leukapheresis or lymphodepleting chemotherapy. If a subject has a positive COVID-19 test, then 2 subsequent negative tests are required, taken at least 7 days apart.

22. 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 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.
23. Pregnant or breastfeeding.
24. In the opinion of the Investigator, the subject is unlikely to fully comply with protocol requirements.

5.4. Screen Failures

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.

5.5. Number of Subjects and Study Duration

Forty-five (45) subjects (90 total subjects) are planned to be dosed separately in both Cohort 1 (synovial sarcoma and MRCLS) and Cohort 2 (synovial sarcoma only). In combination, data from Cohort 1 and Cohort 2 will provide a better, more comprehensive, characterization of the benefit risk profile in soft-tissue sarcoma patients (especially in synovial sarcoma) than from Cohort 1 alone.

Enrollment into Cohort 1 is expected to continue for approximately 12 months and is close to completion at the time of this amendment. Cohort 2 will begin when dosing in Cohort 1 is completed. Cohort 2 will dose 45 advanced (inoperable)/metastatic synovial sarcoma subjects only and enrollment is expected to continue for approximately 12 months. The Primary Clinical Analysis will be for Cohort 1 only (i.e. synovial sarcoma plus MRCLS). Clinical cut-off for the primary analysis will occur once the last subject dosed in Cohort 1 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 from Cohort 1 only 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 the study for any reason.

5.6. Sites

The study will be conducted in approximately 24 sites in North America and Europe. The number of centers is necessary to ensure recruitment in this rare patient population. Additional sites, especially specialist pediatric oncology centers for the conduct of Cohort 2, 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-A2M4.

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

A non-mobilized peripheral blood mononuclear cell (PBMC) collection should be performed by an apheresis unit at the enrolling institution according to the institution's or hospital's policies and procedures. Leukapheresis may be performed at a qualified third-party institution (as may be mutually agreed and approved in advance by both Sponsor and the clinical site), as long as the policies and procedures in place meet or exceed the primary institution's policies and procedures. Bilateral peripheral venous access should be used whenever possible but a temporary central venous catheter (CVC) may be placed for collection if peripheral venous access is inadequate. Standard clinical procedures for apheresis should be followed.

A large volume leukapheresis should be performed. For subjects who are >50 kg, 10 to 15 liters should be processed per procedure; in subjects ≤ 50kg, 2-3 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 calcium chloride and magnesium sulfate 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, may be used by the sponsor for research to modify or improve the manufacturing process and to enhance the clinical response.

Children aged 10-17 years old will undergo leukapheresis under the care of a pediatric apheresis unit, or as per local site policy for older adolescents. Blood volume will be processed as per local site age-stratified policies.

6.2. Lymphodepleting Chemotherapy

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

Once the manufactured ADP-A2M4 cell product has been received at the clinical site and the integrity of the bag(s) has been verified by the site, eligible subjects will proceed to have lymphodepleting chemotherapy with fludarabine and cyclophosphamide as described in Table 3.

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 prophylaxis (see Section 10.5.3.7) in line with institutional guidelines.

Appropriate intravenous (IV) hydration should be administered and Mesna should be given to prevent urotoxicity while cyclophosphamide is administered, as described below. Other premedication (e.g. anti-emetics) may also be provided in accordance with institutional standards. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. Based on real-world use of Granulocyte-colony stimulating factor (G-CSF) prophylaxis in Cohort 1 at the study sites, especially those with extensive CD19 CAR-T cell therapy expertise, G-CSF prophylaxis in Cohort 2 synovial sarcoma subjects can be given at the clinical discretion of the Investigator (as per local institutional policy) starting on Day -3 until resolution of neutropenia in accordance with American Society of Clinical Oncology (ASCO) guidelines or institutional practice (see Section 6.2.3).

Children aged 10-17 years old will undergo lymphodepleting chemotherapy under the care of a pediatric unit, or as per local site policy for older adolescents.

Table 3: Fludarabine and Cyclophosphamide Treatment Schema

Lymphodepleting Chemotherapy				
Day	**Drug**	**Dose**	**Route**	**Administration**
-7	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[3]
-6	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[3]
-5	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
	Cyclophosphamide	600 mg/m^2	IV	in 200-500mL 0.9% NaCl over 1 hour[2]
-4	**Fludarabine**[1]	30 mg/m^2	IV	in 50-100mL 0.9% NaCl over 30 mins[2]
-3	**Start G-CSF**[4]			
-2				
-1				
1	**ADP-A2M4 infusion**[3]			

[1] Fludarabine dose will be adjusted for renal impairment as described in Section 6.2.1
[2] Concentration of 1mg/ml or less
[3] Administration of ADP-A2M4 infusion is described in Section 6.3.
[4] Administration of G-CSF 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
60 – 79 mL/min	20 mg/m^2

Renal function should be estimated using the Cockcroft-Gault Creatinine Clearance (CrCl) equation (no other renal function equations are permitted).

A more sensitive evaluation of renal function using either a 24-hour urine creatinine collection or a EDTA radionuclide test should be performed in subjects at Screening and/or Baseline who are:

- Obese (i.e. BMI ≥ 30 KG/m2)
- Underweight (i.e. BMI < 18.5 KG/m2)
- Low borderline CockCroft-Gault calculated CrCl of approximately 60 ml/min.

6.2.2. Mesna

Mesna should be administered according to institutional practice or as recommended below:

- 120 mg/m^2 (20% cyclophosphamide dose) as an IV bolus pre infusion, 4 and 8 hours post infusion on each day of cyclophosphamide administration.

6.2.3. G-CSF

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

Administration of G-CSF in children in Cohort 2 will be as per local site policy for cell therapies.

6.3. Investigational Product

6.3.1. Premedication

Subjects will be premedicated with antihistamine and acetaminophen/paracetamol 30-60 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.

6.3.2. T Cell Infusion

On Day 1, the subject will receive thawed ADP-A2M4 by intravenous infusion. The T cell infusion will be given as an inpatient procedure and subjects will remain hospitalized for observation for at least 10 days post T cell infusion.

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

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

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

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

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

If after thawing the infusion bag is damaged or leaking, the 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 15-45 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 - 250 ml of 0.9% sodium chloride should be connected to the second lumen of the infusion set, used to prime the line, and then the lumen closed. On completion of the infusion of a bag of T-cell product, the main line should be closed and approximately 50ml saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided.

On completion of the cell infusion the set should be flushed using additional saline from the attached bag. If Institutional practice requires a single spike infusion set (e.g. macro drip IV tubing) standard institutional guidelines for the infusion of autologous cell infusion should be followed. The line must be flushed with 0.9% sodium chloride once the infusion is complete. In the event of adverse reaction to the cell infusion the infusion rate should be reduced and the reaction managed according to institutional standard procedures. Steroid treatment should be avoided unless medically required.

In the event a subject develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia (see Section 10.5.3).

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.

6.4. Preparation/Handling/Storage/Accountability

6.4.1. Packaging and Labelling

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

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

6.4.2. Receipt and Return

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

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

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 investigational product 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 Investigational Product are correctly received by a responsible person
- Such deliveries are recorded
- Investigational product is handled and stored safely and properly as instructed in the Apheresis and T cell Product Manual
- Investigational product is only administered to study subjects in accordance with the protocol
- Investigational product administration is documented. Records must include the identification of the person to whom the investigational product 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 investigational product 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 investigational product in the trial will be provided with an alert card, which has been previously agreed by the sponsor and approved by the institutional review board (IRB)/ independent ethics committee (IEC). Alert cards will contain at a minimum the name of the subject, the investigator contact number and information regarding the investigational product 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 anticancer locoregional therapies such as non-palliative radiation.

Subjects who undergo any active anticancer therapy, with the exception of surgical resection prior to disease progression, will be considered as having met the 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 ADP-A2M4. However, a subject whose tumor becomes resectable and who undergoes surgical resection prior to disease progression, will continue to be followed for safety and efficacy (progression of remaining lesions, new lesions) in the interventional phase of the study until disease progression is determined. Upon progression, the subject will follow the LTFU schedule. Subjects who have surgery for new lesions consistent with progressive disease or to control progressive disease in previously identified lesions will discontinue the interventional phase and follow the LTFU schedule.

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

The use of systemic steroids may abrogate the effects of the T-cell therapy and therefore use is discouraged unless required to manage CRS (see Section 10.5.6 for CRS treatment recommendations) or other significant immune-mediated adverse events. According to local standard of care or ASCO guidelines, steroids may be used as antiemetics 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. 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 and record the disease progression in the eCRF.

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

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

- All prescription and nonprescription medication, vitamins, herbal and nutritional supplements taken by the subject during the 30 days prior to screening (Visit 2) will be recorded at the screening visit.
- All prior anti-cancer treatments taken by the subject must be recorded regardless of time frame taken
- All concomitant medications taken while subjects are in the interventional phase

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 Immunocompromised 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-A2M4 cell infusion, should be discussed with the Medical Monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Temporary Study Suspension

Throughout the conduct of the study, safety data will be reviewed on an ongoing basis by a Data Safety Monitoring Board (DSMB) see Section 10.2.1. If the following events occur, further enrollment to the study will be suspended and the regulatory authorities informed:

- A subject has a positive RCL:
  - Confirmed positive peripheral blood mononuclear cell (PBMC) replication competent lentivirus (RCL) and no other vector lot is available for use in transduction for subsequent subjects (refer to Section 10.7.2 and Figure 1 on monitoring and management of RCL)
  - Confirmed biological RCL - all ADP-A2M4 cell infusions are halted (see 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
- Died
- Unable/unwilling to comply with study requirements
- Withdrawal of consent
- Investigator decision
- Adverse Event
- Lost to follow-up
- Pregnancy (see Section 10.6.2.1)
- Termination of enrollment by the Sponsor

All subjects ending the interventional phase, with the exception of those who withdraw consent, die, are unable/unwilling to comply with study requirements, are lost to follow up or did not receive any T cells, will switch to the LTFU schedule Table 2, Section 1.3.2 to continue observation for delayed adverse events 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 whole 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 withdrawal of a subject from the study are:

- Unable/Unwilling to comply with study requirements
- Adverse event
- Withdrawal of consent
- Investigator decision
- Lost to follow-up (see Section 7.4)
- Study termination by 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

8.1. Background Assessments

8.1.1. Demographics

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

8.1.2. Disease History

The following information will be recorded in the eCRF: date of initial diagnosis, primary tumor type, anatomical site and size of primary tumor, histology last known stage of disease and chromosomal translocations.

8.2. HLA MAGE-A4 Tumor Antigen Testing, and Cytogenetics

There is no window for obtaining HLA, MAGE-A4 antigen and cytogenetic testing 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 approved HLA Sequencing System for Sequence Based Typing (SBT) of Human Leukocyte Antigen (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 subjects' 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 study Sample Collection 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 Sample Collection 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.

8.2.3. Cytogenetics for Diagnosis

For Synovial Sarcoma (Cohort 1 and Cohort 2), a confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t (X; 18)) is required prior to leukapheresis

For MRCLS (Cohort 1 only), a confirmation by the presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) or t(12; 22) (q13;q12) is required prior to leukapheresis.

Cytogenetic confirmation of diagnosis can be historic, done as standard of care, or be done any time after signing the Treatment ICF and does not need to be within the 28-day screening window.

8.3. Efficacy Assessments

8.3.1. CT/MRI

Imaging scans of the chest, abdomen and pelvis should be performed at Screening, 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 independent review, scheduled study 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:

- 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 a non-contrast enhanced CT of the chest, if contrast enhanced CT is contraindicated for a subject
- MRI of the extremities if clinically indicated.
- 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 inflammation'), disease progression will not be determined before 4 weeks post infusion of ADP-A2M4, 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 not 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-A2M4 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 patient care throughout the study.

8.3.2. Survival

If a subject dies during the study date of death will be recorded in the eCRF. 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 Test in Table 5 describe 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 four 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) in the subject's eCRF.

8.4.2. Physical Examination

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

8.4.3. Prior Anti-cancer Therapies

All 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 recorded on the concomitant medication page of the CRF 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 in subjects who are ≥16 years old. See Section 10.9, Appendix 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 assessment is specified in Table 1.

8.4.6. Lansky

Performance status will be measured using the Lansky performance scale in subjects <16 years old. See Section 10.9, Appendix 10 for guidance. It is recommended, where possible, that a subject's Lansky be assessed by the same person throughout the study. The frequency of the Lansky assessment is specified in Table 1.

8.4.7. 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.

8.4.8. Weight and Height

Height will be assessed only once at Baseline. Weight will be measured according to the frequency specified in Table 1.

8.4.9. Cardiac Assessments

Cardiac assessments will be performed locally at the site.

8.4.9.1. ECG

A single ECG is required. Heart rate, rhythm, PR, RR (if measured/recorded), QRS and QTc intervals will be recorded. QTcB or QTcF is acceptable as per institutional standards but must be consistent from visit to visit.

For Screening (Visit 2) ECGs performed as standard of care within 28 days prior the visit are acceptable. The ECG on Day 1 will taken before T cell infusion starts.

8.4.9.2. Echo/MUGA

An ECHO or MUGA scan will be performed at screening to determine left ventricular ejection fraction (LVEF) for eligibility. ECHO/MUGA scans performed as standard of care within four 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 seven days post-ADP-A2M4 infusion.

8.4.10. Brain MRI

A MRI of the brain with contrast will be obtained at Baseline, within 1 month of lymphodepletion, for all subjects. CT with IV contrast may be used only for subjects with

contraindications to MRI of the 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 (see Section 8.3.1). If brain metastases are not documented at Baseline, then dedicated brain CT/MRI scans should be performed as clinically indicated.

8.4.11. Renal Function Assessment

Renal function (estimated or measured glomerular filtration rate (GFR)) will be assessed at Screening using Cockcroft CrCl equation, 24 hour urine collection to measure creatinine clearance or by nuclear medicine EDTA measurement should be performed in subjects who are i). clinically obese adults (i.e. ≥ 30KG/m2); ii). Clinically underweight adults (i.e. ≤ 18.5KG/m2); iii). ≥ 65 years old; iv). Low borderline calculated CrCl ~ 60 ml/min (Cockcroft-Gault).

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

8.4.12. Hematology

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

In years 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 8.4.23) then laboratory assessments may be discontinued.

8.4.13. Clinical Chemistry

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

In years 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 8.4.23) then laboratory assessments are discontinued.

8.4.14. Coagulation

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

Subjects receiving warfarin anti-coagulation at baseline should be converted to either a low molecular weight heparin injection or a novel oral anticoagulant (NOAC). Reintroduction of warfarin after lymphodepleting chemotherapy/ADP-A2M4 dosing to attain the therapeutic INR range which was initially clinically indicated should only start when the platelet count is < Grade 2 CTCAE.

8.4.15. Thyroid Function Tests

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

8.4.16. Hepatic Safety Assessments

For subjects who experience evidence of hepatic toxicity, increased hepatic monitoring criteria will apply to ensure subject safety and to enable evaluation of liver event etiology (see Appendix 4, Section 10.4.5).

8.4.17. Pregnancy Test

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

8.4.18. Infectious Disease Screening

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

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

8.4.19. CMV PCR

Subjects will be screened for cytomegalovirus (CMV) seropositivity at screening. If seropositive at screening, then CMV-PCR will be done at Baseline. 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, week 2, 4, 6, and 8. See Section 10.5.3.4 for CMV prophylaxis and blood product screening if positive.

8.4.20. ICE/CAPD Assessment Tool

Subjects aged ≥ 12 years old: The ICE (Immune Effector Cell-Associated Neurotoxicity Syndrome) neurological assessment should be performed from Day 1 (prior to T cell infusion) through Day 8 whilst the subject is hospitalized according to Table 1 . The ICE assessment may be discontinued once a subject is discharged from hospital.

If a subject is thought to have ICANS, the ICE should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated. See Section 10.5.7, Table 8.

Subjects < 12 years old: The Cornell Assessment Pediatric Delirium Score (CAPD) will be used to monitor for ICANS. See Section 10.5.7, Table 4.

Table 4: CAPD-point neurological assessment [based on Traube, 2014]

RASS Score____ (if -4 or -5 do not proceed)

Please answer the following questions based in your interactions with the patient over the course of your shift:						
	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	Score
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child tale a long time to respond to interactions?						
	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive: very little movement and interaction?						
8. Are the child's responses sparse and/or delayed?						

Scores between 1-8 may represent no impairment, grade 1 or grade 2 ICANS and must be combined with clinical assessment. Score > 8 corresponds to grade 3 ICANS. If unable to perform CAPD due to the patient being unrousable, this would correspond to grade 4 ICANS [Brown, 2021]. Any increase in CAPD score requires increasingly escalating and more frequent neurological monitoring.

8.4.21. C-reactive Protein

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

8.4.22. Ferritin

If cytokine release syndrome is suspected, ferritin levels should be measured approximately every other day with C-reactive protein.

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 8.6.5).

Samples are required for:

- Safety at Baseline and Week 24, Month 12 and then every 6 months through Year 5 and annually from Years 6-15.
    - 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 may be discontinued.
    - 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 (Appendix 6 Section 10.7.3).
- Research at Day 2, Day 4, Day 8, Week, 2, Week 4, Week 8, Week 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 Sample Collection Manual.

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

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

If a positive VSV-G DNA signal is obtained, the study investigator will be informed and the subject will be scheduled for a retest as soon as possible and no later than one month after the

initial positive result was reported to the Sponsor. See Appendix 7 Section 10.7.2 for additional information.

Details on collection and shipment of blood sample for RCL is described in the Sample Collection 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, tumor biopsy) until 24 hours afterwards for blood sampling, or until 2 weeks post-biopsy.
- From date of signing the Treatment ICF 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 discontinues the interventional phase of the study. In addition, emerging clinical conditions defined in Appendix 4, Section 10.4.6 will be monitored for starting Day 1. If the subject has not progressed after 12 months, only those emerging clinical conditions defined in Appendix 4, Section 10.4.6 will be collected thereafter.
- During the long-term follow-up phase of the study, subjects will only be monitored for the emerging clinical conditions defined in Appendix 4, 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 Appendix 4.

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.

8.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4, 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 participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 4, Section 10.4.3.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt (within 24 hours) notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (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 in the form of Investigator Safety Letters (ISL).
- An investigator who receives an investigator safety letter describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and 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 which 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 investigational product. Details of all pregnancies in female participants and female partners of male participants will be collected from the start of lymphodepletion for as long as there is evidence of T-cell persistence, or until the subject has confirmed disease progression.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6. See Section 10.6.2 for guidance.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

The safety of ADP-A2M4 during pregnancy and lactation has not been established in humans. The target antigen is known to be expressed on fetal germ line tissues and placenta, therefore female subjects who are pregnant, intending to become pregnant, or breast feeding are excluded from ADP-A2M4 studies.

There is no preclinical or clinical trial data of ADP-A2M4 in pregnant women; however, there is a reasonable but unproven likelihood that this intervention may be significantly embryotoxic or even an abortifacient given the underlying biology of the target. The effects on breast milk are unknown, therefore breastfeeding should be discontinued for the duration of the study, starting at the first dose of chemotherapy and for at least 12 months after receiving the investigational product, or four months after there is no evidence of persistence/gene modified cells in the Subjects blood, whichever is longer.

The contraception guidelines provided in Section 10.6.1 should continue to be adhered to during long-term follow up.

A woman who becomes and remains pregnant during the study will be discontinued from the-interventional phase as exposure to radiation from imaging studies would be contraindicated. The subject would follow the LTFU T & E schedule 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. AE of Special Interest

8.5.7.1. Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a potentially life-threatening toxicity that has been observed following administration of antibodies and adoptive T-cell therapies for cancer. It is defined clinically by symptoms which 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 seven 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.

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 grading and management of CRS.

8.5.7.2. Neurotoxicity

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 cytokine release syndrome (CRS) symptoms. This form of ICANS tends to be of shorter duration, lower grade (Grade 1–2, see Table 9), 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 CART‑cell therapy, after the initial fever and CRS subside [Lee, 2019].

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

8.5.7.2.1. Monitoring for ICANS

The ICE is a neurological assessment tool for subjects aged ≥ 12 years old which is used to assess cognitive function to monitor for ICANS (see Section 10.5.7 for details). ICE or Cornell Assessment Pediatric Delirium Score (for subjects < 12 years old) should be measured on the day of ADP-A2M4 infusion prior to receiving treatment and through Day 8 whilst the subject is hospitalized. If the subject is discharged before Day 8 the ICE or Cornell Assessment Pediatric Delirium Score may be discontinued according to the T&E Table (Section 1.3.1). Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following ADP-A2M4 infusion if hospitalized. If a subject is found to have ICANS, the ICE or the Cornell Assessment Pediatric Delirium Score 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. ICE and the Cornell Assessment Pediatric Delirium Score also forms part of the grading system for ICANS developed by [Lee, 2019].

ICANS is graded and managed according to the severity of symptoms, see Section 10.5.8 for detailed guidance on management of ICANS.

8.5.8. Long Term Follow Up Adverse Events

During the long term follow-up (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 Letters 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 (Appendix 7, 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 T&E Table (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 should be collected within two months of the T cell infusion, with preference for a biopsy to be taken closer to the time of infusion. Tumor tissue should either be taken from non-target lesions or from target lesions where sampling can be done without 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).

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 collected obtained post-progression (e.g. from an excisional surgery).

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

8.6.2. Cytokine and Soluble Protein Analysis

Serum is collected at Baseline, pre-infusion and 2-4 hours post infusion on Day 1 and on Day 2, Day 4, Day 8, Week 2, 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 Sample Collection Manual.

Serum samples may also be used to detect humoral immune responses to tumor antigens and antibodies to ADP-A2M4.

8.6.3. [redacted]

[redacted]

8.6.4. [redacted]

[redacted]

- [redacted]

8.6.5. Persistence of ADP-A2M4 TCR+ 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]
- [redacted]

8.7. Blood Sampling Volumes

The amount of blood drawn for research purposes from pediatric subjects (those under 18 years of age or relative country-specific guidelines) will not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time as specified in Ethical considerations for clinical trials on medicinal products conducted with minors (2017). To comply with European Recommendations in pediatric subjects biomarker Research Blood draws (cytokine, liquid biopsy and cell phenotyping samples) will not be collected as part of this protocol.

Body Wt (Kg)	Circulating Blood volume (ml)	Maximum allowable sample volume over 4 weeks (ml) - 3% of total blood volume	Maximum allowable sample volume at single time (ml) - 1% of total blood volume
30-70	2400- 5600	48 – 168	24 – 56

In the event that blood draws are limited due to these restrictions, blood samples will be collected in order of priority as defined in the Laboratory Manual.

8.8. Patient-Reported Outcomes

8.8.1. 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, 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 (VAS) 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 Month 12. Once disease progression is established, the EQ-5D-3L assessment is no longer required.

8.8.2. EORTC-QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed by the Quality of Life Group of the European Organisation for Research and Treatment of Cancer to assess the quality of life of cancer patients. It can be used for patients ≥ 18 years old in Cohort 2.

The EORTC QLQ-C30 will only be used in synovial sarcoma subjects in Cohort 2 at Baseline and post T-cell infusion at Week 8, Week 16, Week 24 and Month 12. Once disease progression is established, the EORTC QLQ-C30 assessment will no longer be required.

The EORTC QLQ-C30 comprises 30 questions. Each of the first 27 questions has 4 levels: Not at All, A Little, Quite a Bit, and Very Much. The respondent is asked to indicate his/her health state by selecting the most appropriate statement. Questions 29 and 30 records the respondent's self-rated health on a horizontal scale where the endpoints are labelled 'Very Poor' and 'Excellent'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

8.8.3. PedsQL™

The PedsQL™ is a questionnaire developed by the Mapi Research Trust to assess the quality of life of pediatric cancer patients.

The PedsQL™ will only be used in synovial sarcoma subjects in Cohort 2 and 10 -17 years of age at Baseline and post T-cell infusion at Week 8, Week 16, Week 24 and Month 12. Once disease progression is established, the PedsQL™ assessment will no longer be required.

The PedsQL™ comprises 27 questions. Each of the 27 questions has 5 levels: Never, Almost Never, Sometimes, Often, and Almost Always. The respondent is asked to indicate his/her health state by selecting the most appropriate statement. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

9. STATISTICAL CONSIDERATIONS

The objectives and endpoints for this study are described in Section 3, this section focusses on key aspects for 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). The analysis plan for the objective related to the development of the validated Companion Diagnostic (CDx) will be described in a separate document. Similarly, 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.

The primary analysis will be for Cohort 1 only 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-A2M4) in Cohort 1.

The primary endpoint for efficacy is Overall Response Rate (ORR) in Cohort 1, defined as the proportion of subjects with a confirmed CR or PR relative to the total number of subjects in the analysis population.

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

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

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

- The historical ORR for Synovial Sarcoma ≤13% and for MRCLS <10% (Section 4.2)
- The ORR for historical control that will be used for hypothesis testing in this study will be 18%.
- The mechanism of action for the TCR is assumed to be the same for synovial sarcoma and MRCLS.
- Section 2.2.3 states that in subjects with synovial sarcoma, the observed ORR (confirmed responses) for ADP-A2M4 cell therapy was 40.0% at the time of data cut off. Therefore,

for purposes of sample size computation, we assumed ORR for ADP-A2M4 cell therapy would be 40%.

- No formal hypothesis testing is planned for Cohort 2 or across cohorts (overall).

The hypothesis of interest for the primary endpoint is;

(Null Hypothesis) H_0: $p \leq p_0$, vs. (Alternate Hypothesis) H_1: $p > p_0$, where p_0 (historical control rate) = 0.18.

Based on above assumptions, the TCR ORR (i.e., p_1) is set at 0.4. The type I error (α) for this test will be no more than 0.025 and the type II error (β) will not exceed 0.1. Exact Binomial methods will be used to test the hypothesis.

Statistical Design Assumptions:

- The assessment for efficacy will be based on the mITT population using confirmed ORR via RECIST v1.1 per independent review in Cohort 1;
- The type I error (α) for this test will be no more than 0.025;
- The type II error (β) will not exceed 0.1;
- Exact Binomial method will be used to test the hypothesis;
- Cohorts 1 and 2 are independent;
- Pediatric subjects in Cohort 2 will not be considered separately to adults. Further, it is assumed that the ORR for pediatric subjects is the same as adults for design considerations.

Based on the statistical design assumptions above and the hypotheses and clinical assumptions in Section 4.2, the estimated sample size for the trial is 45 subjects in Cohort 1.

The ORR for Synovial Sarcoma ranges between 4% – 13% in clinical trials (Section 2.2.3). If we assume that the ORR of the ADP-A2M4 will be 40% (P1), and historical ORR (P0) is 13%, a sample size of N=27 provides 90% power to detect an absolute difference of 27% using exact binomial assumptions.

To account for the potential variability in historical control efficacy, a more conservative historical ORR of 18% may also be considered. Using a one-sided alpha=0.025, if we assume that the ORR of ADP-A2M4 will be 40% (P1) and historical ORR may be as high as 18% (P0), a sample size of N=45 in Cohort 1 provides at least 90% power to detect a difference of 22% using exact binomial assumptions.

The following table describes samples sizes for a single cohort under a range of assumptions for the exact binomial assumption as described above.

Historical ORR (P0)	TCR ORR (P1)	Difference (P1-P0)	N
0.13	0.40	0.27	27
0.13	0.45	0.32	21
0.15	0.40	0.25	33
0.15	0.45	0.30	24
0.15	0.50	0.35	19
0.18	0.40	0.22	45
0.18	0.45	0.27	32
0.18	0.50	0.32	21

Based on these evaluations, the sample size is 45 subjects in Cohort 1 for the primary analysis.

Additional subjects are enrolled in Cohort 2 to supplement Cohort 1 with additional safety and efficacy data based on clinical judgement. No formal hypothesis testing is planned for either Cohort 2 or overall. One benefit of these additional subjects (irrespective of whether adult or pediatric subjects) is an increase in precision for ORR by assessing the endpoint across cohorts, and thus in a larger sample of subjects. The following table summarizes the width (point estimate – lower bound) of a 97.5% one-sided confidence interval using exact binomial methods for different sizes of Cohort 2. Also provided for context is the probability that the lower bound of the confidence interval exceeds p0=18% for different sizes for Cohort 2. The assumed TCR ORR is 40%.

Size of Cohort 2	Size of Overall (across cohort)	CI Width	Probability CI LB > 0.18
0	45	0.143	0.916
15	60	0.124	0.959
30	75	0.111	0.989
45	90	0.102	0.994

Based on these evaluations, enrolling an additional 45 subjects in Cohort 2 reduces the width of the confidence interval by about 28% [(0.143-0.102)/0.143] compared to the expected confidence interval width when only using Cohort 1. Further, if the TCR ORR is 40% the

probability that the lower bound of the confidence interval exceeds 18% increases from about 92% when only using Cohort 1 subjects to greater than 99% if 45 subjects are enrolled in Cohort 2. These results support enrolling an additional 45 subjects in Cohort 2, for a total of 90 subjects across cohorts.

9.3. Statistical Analyses

The statistical analysis plan (SAP) document will provide full details about data derivations and displays and analysis methods for primary, secondary and exploratory endpoints. This section captures key aspects of the analysis.

Demography and baseline characteristics will be summarized using appropriate descriptive statistics. Subject disposition including number of subjects leukapheresed, lymphodepleted and treated with ADP-A2M4 will be summarized. Reasons for subject discontinuation from the study will be displayed.

9.3.1. Interim Analysis

There is no interim analysis planned.

9.3.2. Efficacy Analyses

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

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

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).

The primary endpoint, ORR per RECIST v1.1 by independent review in Cohort 1, will be evaluated using a one-sided exact-based Clopper-Pearson 97.5% confidence interval (CI). If the lower bound of the 97.5% CI exceeds 18%, the trial has met the pre-specified threshold for demonstrating efficacy and the trial has met the criterion for statistical significance.

As a sensitivity analysis, one-sided 97.5% confidence interval using the Wilson method may also be provided.

ORR per RECIST v1.1 by independent review will also be evaluated across cohorts (overall).

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.
- Duration of Response (DoR), defined as the duration from the initial date of the confirmed response to the date of progressive disease or death.

- Progression Free Survival (PFS), defined as the interval between the date T-cell infusion and the earliest date of disease progression based on RECIST v1.1 or death due to any cause.
- Overall Survival (OS), defined 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 DoR and PFS. As a sensitivity analysis, determination of progression (via RECIST v1.1) using lesion assessments will also be provided.

All secondary efficacy endpoints will be summarized for Cohort 1 and across cohorts (overall).

No hypothesis testing is planned for these secondary endpoints in Cohort 1 or across cohorts. Time to event endpoints (i.e., OS and PFS) will be summarized and displayed graphically using Kaplan-Meier (K-M) methodology to estimate the median, and the 25^{th} and 75^{th} percentiles. Two-sided 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.

The following censoring rules will be applied:

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

The proportion of censored observations will be summarized.

The pharmacokinetic (PK) profile 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.

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 also include the per protocol (PP) population. All safety analyses will be summarized for Cohort 1 and across cohorts (overall).

The safety profile will be based on adverse events, serious adverse events, replication competent lentivirus (RCL) and vector integration/clonality. 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.

Adverse events will be summarized using two time periods:

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

Adverse events throughout the trial will be coded by MedDRA v21.0 or higher. The number and percent of subjects reporting any adverse events will be tabulated by system organ class and preferred term. Adverse events 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., cytokine release syndrome (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 electronic Case Report Form (eCRF). Within the EDC system the eCRF data will be entered by the site staff and all source document verification and data cleaning will be performed by the Sponsor or designee (e.g. CRO).

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

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

Standard coding dictionaries, WHO Drug and MedDRA will be used to code medications and adverse events.

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

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

10.1.1.2. Case Report Forms

For each subject enrolled, the completed eCRF must be reviewed and signed by the Principal Investigator or authorized delegate. If a subject discontinues 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, investigational product handling and accountability, presence of required documents, the informed consent process and comparison of eCRFs with source documents.

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

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

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

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and any other site level committee deemed appropriate by the Institution. Approval from each applicable committee will be received in writing before initiation of the study.

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

10.1.3.3. Local regulations/Declaration of Helsinki

The Investigator will ensure this study is conducted in full compliance with the principals of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever, affords the greater protection to the subject. The study must fully adhere to the principles outlined in 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 consent form should be translated and communicated to the subject in a language that is understandable to the subject. Certified translations of the informed consent documentation will be provided as applicable.

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

Tests performed as standard of care prior to documentation of consent may be used for screening results as appropriate (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 (CSR) according to ICH guideline E3: Structure and Content of Clinical Study Reports.

10.1.10. Publication Policy

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

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

10.1.11. Financial Disclosure

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

10.2. Appendix 2: Safety Reviews

10.2.1. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be implemented for this study for Cohort 1 only 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 after approximately 5, 15, and 30 subjects have been dosed. At the time of Protocol Amendment 3, the DSMB has held 2 operational meetings to review data from after dosing of 5, and 15 subjects. Both meetings resulted in the DSMB recommendation to continue the study without protocol modification.

At the time of Protocol Amendment 4, the final/3rd DSMB meeting was held in March 2021 after the 30th subject was dosed in Cohort 1. The decision from the DSMB was to continue the study with no safety modifications since the emergent benefit-risk profile was favorable.

10.2.2. Safety Review Committee

A Safety Review Committee (SRC) will be implemented in Cohort 2 of this study to review pediatric safety data in subjects < 16 years old, and will consist of at least 3 external physicians including 1 with expertise in pediatric oncology, at least 1 of whom is unaffiliated to the studies, the Sponsor Pharmacovigilance Physician, the Sponsor Head of Clinical Development, and the Sponsor Head of Statistics.

The SRC can be convened by the discretion of the Adaptimmune pharmacovigilance team at any time during the conduct of Cohort 2 based on emergent safety findings in subjects < 16 years old.

The SRC will use clinical judgment to assess the benefit:risk of the study in the pediatric subjects < 16 years old, and will recommend actions regarding study modification for safety reasons, halting and restarting pediatric enrollment, termination of pediatric recruitment in Cohort 2, or any other safety-related issues

A SRC charter, defining objectives, roles, accountabilities, meeting frequency, and the process for safety review, is available.

10.3. Appendix 3: Clinical Laboratory Tests

Table 5: Protocol-Required Safety Laboratory Assessments

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

Hematology:	Red blood cell count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Mean cell volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Reticulocytes (absolute) Platelet count White blood cell count (WBC) 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 (ALK) Lactate dehydrogenase (LDH) Sodium Potassium Bicarbonate Creatinine Chloride Glucose BUN or Urea
Other Tests:	Ferritin C-reactive protein

Coagulation Screen:	Prothrombin time (PT) *or* International Normalized Ratio (INR) Activated partial tissue thromboplastin time (aPTT)
Pregnancy Test:	Serum beta-HCG or Urine test[1]
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[#] EBV (EBNA)[#] Treponema IgG or RPR [#] **Viral reactivation** CMV DNA PCR – peripheral blood for detection of reactivation. In the event of suspected end organ CMV disease a biopsy may be required [#] Per Institutional Standard Practice is acceptable

[1] Not required for pre-pubertal girls

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

Events <u>Meeting</u> 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 fulfil the definition of an AE or SAE.

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

10.4.2. 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).

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

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

g. Additional protocol-defined criteria

- Any Grade ≥3 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 (see Section 10.4.5):
  - ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)
  - ALT ≥3xULN 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 CRF.
- 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 CRF 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 will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 5.0. See Section 10.5.6 and 10.4.7 for guidance on grading of CRS and ES respectively. For AEs not specifically listed in the CTCAE, The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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.

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.

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.

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 CRF.
- 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 SAE worksheet (SAEW) within 24 hours of the study personnel's discovery of the event.
• Complete the SAEW as fully as possible and obtain the Investigators signature. Create a PDF of the signed SAEW and submit to:
  • [redacted]
  • [redacted]
• Do not delay reporting an SAE if the Investigator is unavailable to sign. Report the SAE as above and provide a copy of the signed SAEW as soon as possible afterwards.

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 Time and Events Table (Section 1.3), 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 (see 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 ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[1]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[2]	ALT ≥3xULN 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 electronic case report form (eCRF), and a serious adverse event worksheet	• Viral hepatitis serology[3]

(SAEW) if the event meets the criteria for an SAE within 24 hours.[1] • Consider hepatologist consultation • Repeat liver chemistry tests (include ALT, AST, ALK, 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 ≥2xULN	• Serum CPK and LDH • CBC with differential to assess eosinophilia • PBMC blood sample for persistence[4] • Assess for the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) and alcohol use • **For bilirubin or INR criteria:** • Hepatologist consultation required • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) • Consider liver biopsy

1. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.
2. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
3. Includes:Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
4. Record the date/time of the PBMC blood sample draw on the CRF. 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, 2006; FDA, 2010; EMA, 2009]. Subjects will be followed according to the schedule outlined in

Section 1.3.2 , 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 to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled, and submitted within the annual report of the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment.

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, cytokine release syndrome, 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 is recommended in all subjects. G-CSF (i.e., filgrastim) should be used for management of neutropenia according to ASCO guidelines [Smith, 2015]. G-CSF should be given on Day -3 until resolution of neutropenia (reaching an ANC of at least 2×10^9/L to 3×10^9/L or as per institutional practice).

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

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-A2M4 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-A2M4 cell infusion.

10.5.3.2. Pneumocystis carinii Pneumonia

Subjects should receive prophylaxis against Pneumocystis pneumonia with drug, dose and duration according to institutional guidelines. Single strength trimethoprim sulfamethoxazole daily is the recommended first line agent, starting at day 28 for one year. Other regimens including atovaquone (1500 mg daily with food) or aerosolized pentamidine (300 mg every four weeks) are also acceptable, e.g. sulfonamide allergy, and 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 HSV episodes.

10.5.3.4. Cytomegalovirus

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. If CMV viremia is detected at baseline, treatment should be initiated and evidence of viral clearance obtained, prior to lymphodepletion chemotherapy. All CMV seropositive subjects will continue to be monitored for CMV viremia by CMV DNA PCR as shown in Table 1 until 60 days post infusion of ADP-A2M4. 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 10.5.9.

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 (300mg daily), entecavir (0.5mg daily), or tenofovir (300mg 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 antifungal 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 x10^9/L, Hb > 8.0 g/dL (or in accordance with institutional practice) and as clinically indicated. See AABB Guideline on platelet transfusion [Kaufman, 2015].

10.5.4.1. 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 allogeneic 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.

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 PI should be contacted and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the ADP-A2M4 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

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 many of which mimic infection including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash and dyspnea. It is important to evaluate the subject for concurrent infections. Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure and disseminated intravascular coagulation. CRS may also be associated with findings of macrophage activation syndrome or occur coincident with tumor lysis syndrome.

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

Table 7 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical, and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels (Section 8.6.2) ferritin (Section 8.4.22), as well C-reactive protein (CRP) (Section 8.4.21) levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 7: Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment	Management Guidelines
1	Constitutional symptoms not life-threatening (e.g., fever, nausea, fatigue, headache, myalgias, malaise)	• Vigilant supportive care[1] • Assess and treat for possible infection[2] • Consider anti-IL-6 therapy[3] (tocilizumab 8 mg/kg* IV) if clinically indicated (i.e., subjects with symptoms persisting ≥ 24 hours or subjects with co-morbidities or subjects of older age)
2	Symptoms require and respond to moderate intervention (Hypotension responds to fluids or one low dose pressor, hypoxia responds to <40% O_2, and/or Grade 2 organ toxicity)	• Monitor cardiac and other organ function • Vigilant supportive care[1] • Assess and treat for possible infection[2] • Treat hypotension with fluid and pressors. • Administer O_2 for hypoxia. Administer anti-IL-6 therapy[3] (tocilizumab 8 mg/kg* IV) at any time if clinically indicated (i.e., subjects with symptoms persisting ≥ 24 hours, or subjects with co-morbidities or subjects of older age)

3	Symptoms require and respond to aggressive intervention hypotension requires multiple pressors or high dose pressors hypoxia requires ≥40% O^2, Grade 3 organ toxicity or Grade 4 transaminitis	• Monitor subject very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). • Vigilant supportive care[1] • Assess and treat for possible infection[2] • Treat hypotension with fluid and pressors. Administer O_2 for hypoxia. • Administer anti-IL-6 therapy[3]
4	Life-threatening symptoms Grade 4 organ toxicity (excluding transaminitis)	• Manage subject in ICU • Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required • Administer anti-IL-6 therapy[3]
5	Death	

1. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure
2. Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of antimicrobial agents for concurrent bacterial infections, and for treatment of fever and neutropenia as per institutional practice; and antipyretics, analgesics as needed.
3. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first line treatment (tocilizumab 8 mg/kg* IV).

   *The maximum dose for tocilizumab is 800 mg per dose. Corticosteroids can be used for subjects refractory to anti IL-6 therapy. Other immunosuppressor agents may also be used, including TNFα and IL-1R inhibitors. Please see text below for details.

Source: Lee, 2019; Neelapu, 2018

Management of children with CRS should be guided by the pediatric cell therapy team with multi-disciplinary involvement where deemed clinically necessary from pediatric Investigators and other specialists especially for serious adverse events, or those refractory to tocilizumab. Age based management of CRS-related hypotension or hypoxia should follow local pediatric guidelines, and/or those outlined by Mahadeo et al [Mahadeo, 2019].

For subjects requiring immunosuppressive intervention anti-IL-6 therapy should be the first line treatment. Tocilizumab is a humanized anti-IL-6 receptor antibody that has been approved for the treatment of CRS. Anecdotally, tocilizumab has produced rapid and complete correction of CRS with single doses [Maude, 2014]. The United States product insert (USPI) for tocilizumab recommends a dose of 8 mg/kg administered over 1 hour in adult subjects as the first-line treatment of severe CRS. Subjects may receive a repeat dose(s) if clinical signs and symptoms do not improve at least 8 hours apart. Refer to Section 10.5.7 below for subjects experiencing Immune Effector Cell-Associated Neurotoxicity Syndrome concurrent with CRS.

Second-line, tocilizumab refractory, management of CRS is at the discretion of the Investigator following local institutional policy. This can potentially include the use of corticosteroids either in combination with a second dose of Tocilizumab [Maus, 2020] or a corticosteroid administered as a single agent after two doses of Tocilizumab have been administered and if CRS symptoms are persisting. Use of steroid sparing agents (e.g. siltuximab or anakinra) is at the discretion of the Investigator.

Lee [2019] recommend steroids as second-line therapy for CRS as the response to anti-IL-6 therapy may be more rapid and owing to the potential of steroids to attenuate the anti-tumor effects of the adoptive T cell therapy. However, in subjects with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability (See Section 10.5.7) or other life-threatening symptomatology, consideration may be given to the use of corticosteroids as immunosuppressive therapy. High doses (e.g. 2 mg/kg/day prednisone equivalent) may be required.

If cytokine release syndrome is suspected, a physician with expertise in the management of subjects following bone marrow transplant should be consulted. If high dose corticosteroids are required, treatment should generally be continued until resolution to Grade 1 followed by tapering doses over several weeks.

Please refer to the most recent version of the product label for tocilizumab and the latest Society for Immunotherapy of Cancer (SITC) guidelines for CRS [e.g. Maus, 2020].

10.5.7. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

See Section 8.5.7.2 for a description of ICANS. Neelapu, et al [Lee, 2019] have developed a grading system for ICANS which incorporates the Immune Effector Cell-Associated Encephalopathy 10‑point neurological assessment (ICE) tool, see Table 8. Points are assigned for each of the tasks in Table 8 which are performed correctly. Normal cognitive function is defined by an overall score of 10.

The ICE should be used to monitor subjects ≥ 12 years old for ICANS. In subjects < 12 years old The CAPD should be used to monitor ICANS, see Table 4.

Table 8: ICE-point neurological assessment [based on Lee, 2019]

Task	ICE Points
Orientation: Orientation to year, month, city, and hospital,	Total of 4 points (one point for each)
Naming: Ability to name three objects(e.g. point to: clock, pen, button)	Total of 3 points (one 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 score is used in grading of ICANS as presented in Table 9**Error! Reference source not found.**.

Table 9: Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score[1]	7–9	3–6	0–2	0 (patient is unarousable, and unable to perform ICE)
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizures	NA	NA	Any clinical seizure, focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Motor findings [3]	NA	NA	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	NA	NA	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

Source: Based on Lee, 2019

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

[1] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE 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.

10.5.8. Management of ICANS

The recommended management of ICANS should be based on toxicity grade. Table 10 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. For subjects with neurologic symptoms refractory to anti-IL-6 therapy, management should follow local cell therapy policies/investigator discretion including the use of corticosteroids.

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 10: Management of ICANS

Grade	Treatment
1	For all patients: • Vigilant supportive care; aspiration precautions; intravenous (IV) hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired • Avoid medications that cause central nervous system depression • Evaluate for other contributing causes and treat accordingly Unless symptoms are mild and transient (e.g. 1 point change in ICE for less than 12 hours): • Neurology consultation including funduscopic exam to assess for papilledema • MRI of the brain with and without contrast (CT scan of the brain if MRI is not feasible). Further testing if indicated such as diagnostic lumbar puncture with measurement of opening pressure if increased intracranial pressure is suspected, or MRI spine if the subject has focal peripheral neurological deficits • Institute levetiracetam therapy and consider EEG if seizure activity is suspected • Consider anti‑IL‑6 therapy with tocilizumab 8 mg/kg[1] IV if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent CRS
2	• Supportive care and neurological work‑up as described for grade 1 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 patient 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 (CSF) opening pressure <20 mmHg should be treated with a corticosteroid regimen as per Grade 4 below. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 ICANS

Grade	Treatment
4	• Supportive care and neurological work‑up as indicated for grade 1 ICANS • Consider neurosurgical consultation for patients with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection • Anti‑IL‑6 therapy and repeat neuroimaging as described for grade 3 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 800mg

Management of children with ICANS or other suspected neurotoxicities should be guided by the pediatric cell therapy team with multi-disciplinary involvement where deemed clinically necessary from pediatric neurologists, intensivists, and other specialists especially for serious adverse events, or those refractory to first-line immunosuppression [Mahadeo, 2019].

10.5.9. Management of Prolonged Cytopenia

10.5.9.1. Definition of prolonged cytopenia, pancytopenia and plastic 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 EU SmPC; KYMRIAH USPI; YESCARTA EU SmPC; YESCARTA UPSI; TECARTUS SmPC; TECARTUS USPI; BREYANZI USPI]. 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 a hypocellular bone marrow when 2 of the following 3 blood counts are met: Absolute Neutrophil Count < 500/µL, Absolute Reticulocyte

Count < 60,000/µL, and Platelet Count < 20,000/µL with the exclusion of myelodysplastic syndrome.

Subjects may be symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. 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.

10.5.9.2. 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, and 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 (ATG), cyclosporine, eltrombopag) as well as antimicrobial prophylaxis/therapy with the advice of your Hematology/Infectious Diseases consultant(s). If high dose corticosteroids are initiated, duration of therapy and taper should be determined with advice from expert consultants.

Management of prolonged cytopenias in children should be guided by a pediatric haematologist with expertise in cell therapy/stem cell transplantation following the above guidelines.

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:

- Female subjects of childbearing potential (FCBP) must agree to use an 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.
- 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 continuing 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 long-term follow up.

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-A2M4.
- 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)

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

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

10.7.1.2. Insertional oncogenesis

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidance [FDA, 2006a; FDA, 2006b; EMA, 2009]. Insertional oncogenesis is a theoretical risk in T cells transduced with a lentiviral vector. T cells appear resistant to transformation by integrating viruses [Cattoglio, 2010; Newrzela, 2008]. However, there are cases of oncogenesis with γ-retroviral transduced stem cells. Four of nine subjects with X-linked severe combined immunodeficiency (SCID-X1) treated with retrovirus transduced stem cells were found to have insertion near the LMO2 proto-oncogene promoter, leading to aberrant transcription and expression of LMO2 which resulted in acute T-cell lymphoblastic leukemia [Hacien-Bey-Abina, 2003; Hacien-Bey-Abina, 2014]. Additionally, two subjects treated for X-linked chronic granulomatous disease (X-CGD) with retroviral transduced stem cells demonstrated insertional activation of the EVI1 transcription factor which resulted in genetic instability, monosomy 7 and clonal progression toward myelodysplasia [Stein, 2010].

10.7.2. Testing for RCL and Persistence

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. The scheme for RCL testing is presented in Figure 1 below. RCL testing and monitoring will take place on subject's peripheral blood mononuclear cells (PBMCs) which will be collected at Baseline and then at 3, 6, and 12 months post-infusion and annually from year 2-15. Samples will be tested for the presence of VSV-G DNA copies.

If all samples are negative in year one, PBMC samples will be collected and archived annually until 15 years 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. The DSMB will be notified and a review by Adaptimmune's Safety Review Team and Safety Governance Board will take place.

Response to potential outcomes of second test:

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

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

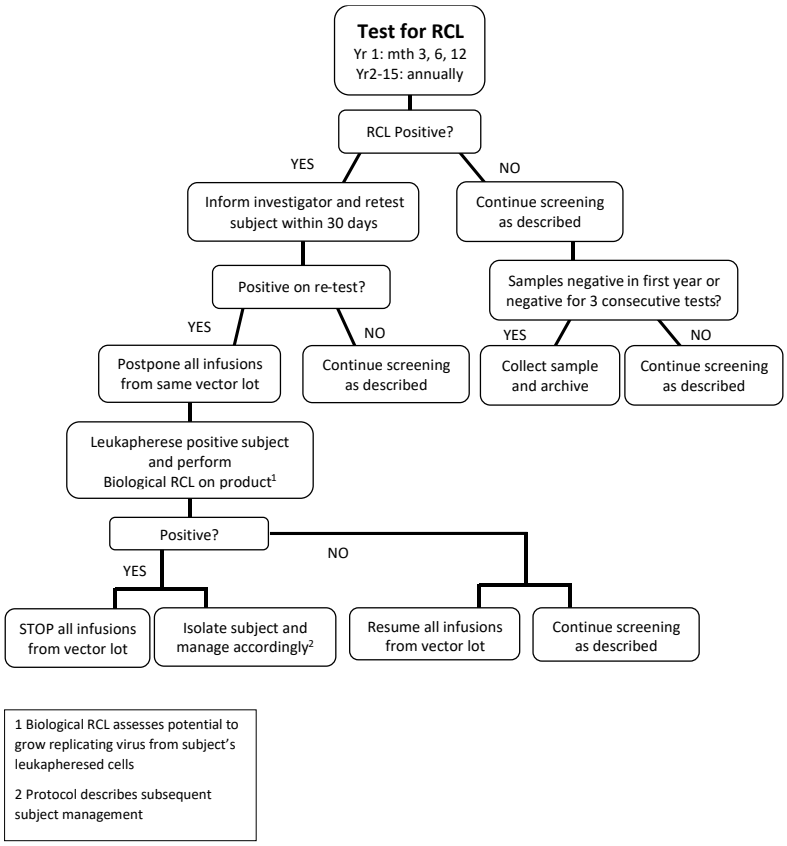
If the biological RCL test is negative, infusions for all subjects can resume.

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

The following approaches have been discussed for subject management:

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

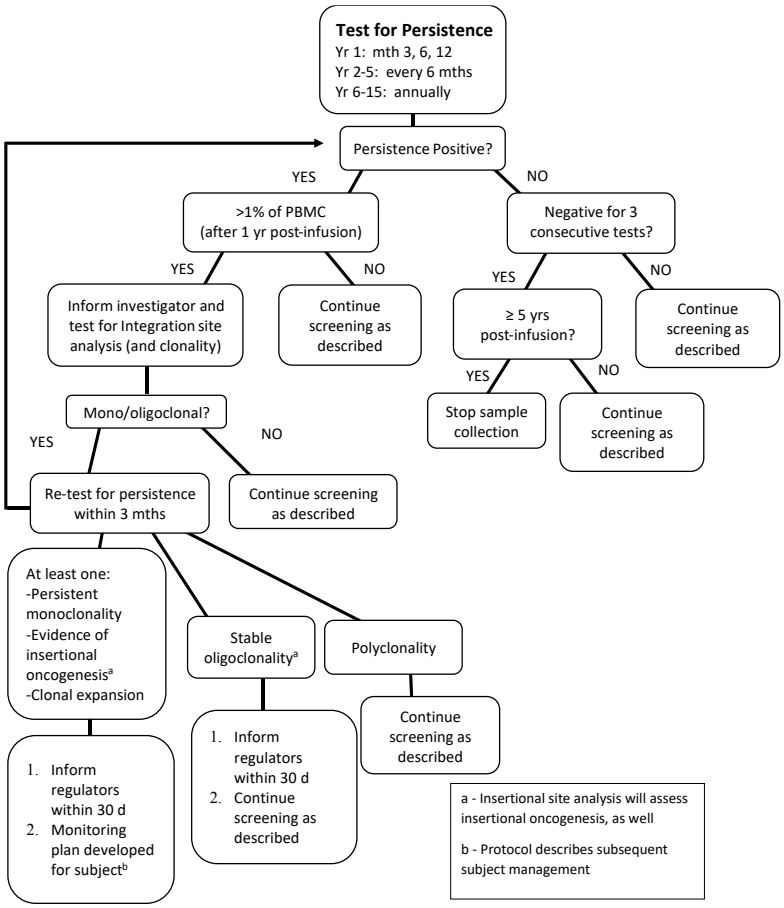
Figure 1: Flow chart for testing for Replication Competent Lentivirus (RCL)



PBMC samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects. Subject samples will be tested for persistence at 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, 2006a; FDA, 2006b; EMA, 2009]. The scheme for testing for persistence is presented in Figure 2.

The samples will be tested using a PCR-based method to detect the presence of the integrated vector sequences Psi DNA, both of which are part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion, greater than 1% PBMCs test positive for vector sequences, the subject's PBMCs will be evaluated for integration site analysis (see 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 insertional oncogenesis.

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

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

monitoring plan specific to the health care risk and strategies to inform appropriate subjects, investigators, FDA and other regulators of the findings.

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

10.7.4. Letter to Physician – LTFU notification

[date]

[name and address]

Dear [physician name],

Your patient [patient name] has participated in a clinical research study, [interventional study name and number], that requires 15 year monitoring for adverse events. To aid in reporting of adverse events that are possible related to the clinical research study, we are asking the patients on our research study to designate a primary care or infectious disease physician that may help in the monitoring and reporting of adverse events. Your patient has designated you. If upon any of your visits with your patient, any of the following events are reported or discovered, please contact the study nurse or physician as soon as possible:

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

If your patient experiences any of these events, please refer them back to their study physician. Please contact the study coordinator below as soon as you can so that they can record the event and then monitor your patient's health if necessary. When you call, remember to mention the protocol number of the study which is ADP-0044-002, patient ID [XXX] and the study title which is "A Phase 2 Single Arm Open-Label Clinical Trial of ADP-A2M4 SPEAR™ T cells in subjects with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma"

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 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 with contrast is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Ultrasound (US) should not be used to measure tumor lesions. The same modality should be used when comparing or making assessments.

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

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

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

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

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

Measurable lesions

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

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

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

Non-target Lesions

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

Evaluation of Target Lesions

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

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

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

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

Special notes on the assessment of target lesions:

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
- Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.
- Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

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

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

Non-CR/Non-PD:

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Special notes on assessing progression of Non-Target lesions

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

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

New lesions

The appearance of new malignant lesions denotes disease progression:

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

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

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

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

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

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required**[1]
CR	CR	No	CR	≥4 wks. Confirmation[2]
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation[3]
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. from ADP-A2M4 infusion
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 for further details on what is evidence of a new lesion [Eisenhauer, 2009]
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. Confirmation of response is established by no evidence of disease progression at the subsequent time point. 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 Non-evaluable Designation

When no imaging/measurement is done at all at a particular time point or the imaging is technically unreadable, 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.

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

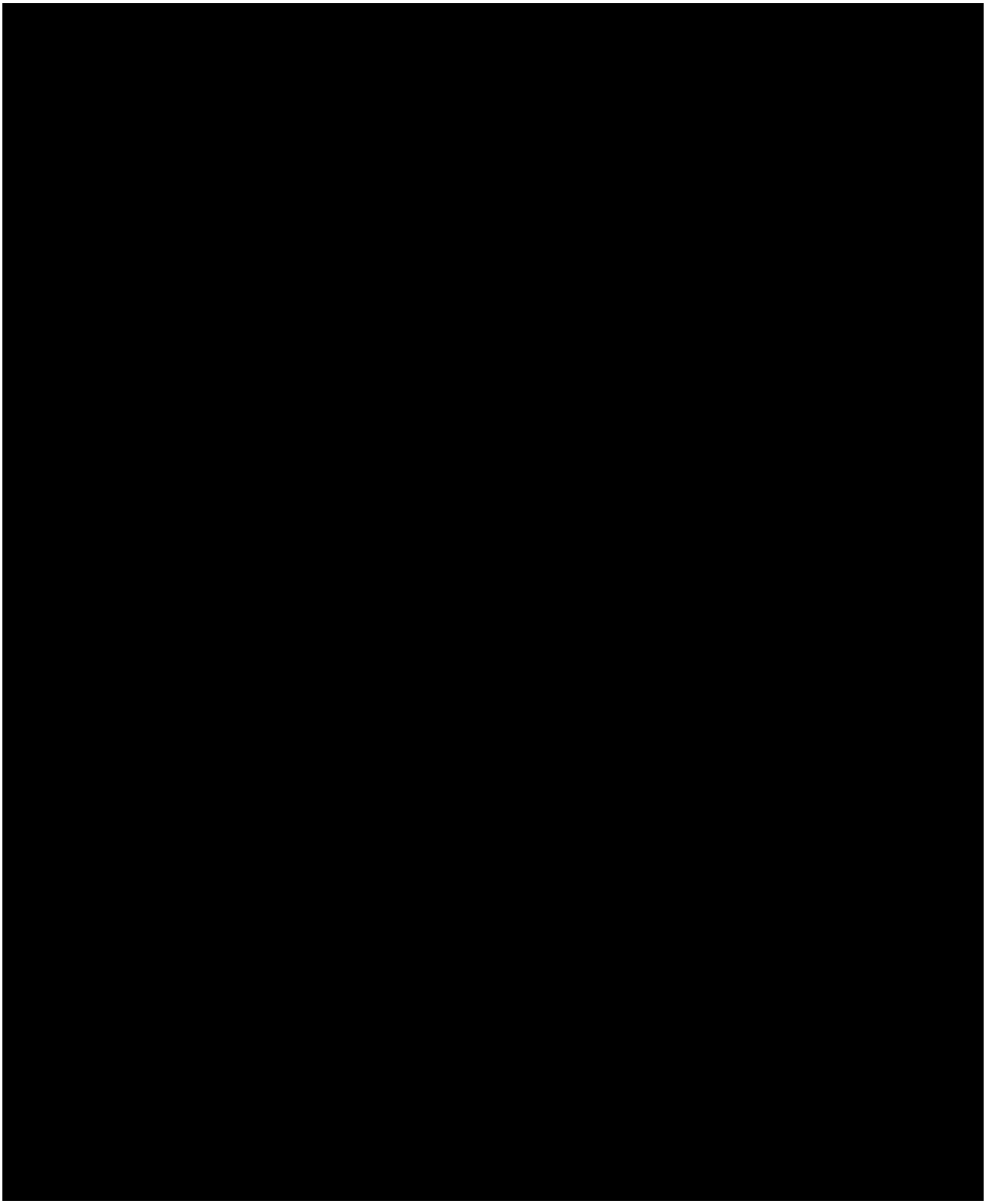
[Oken, 1982]

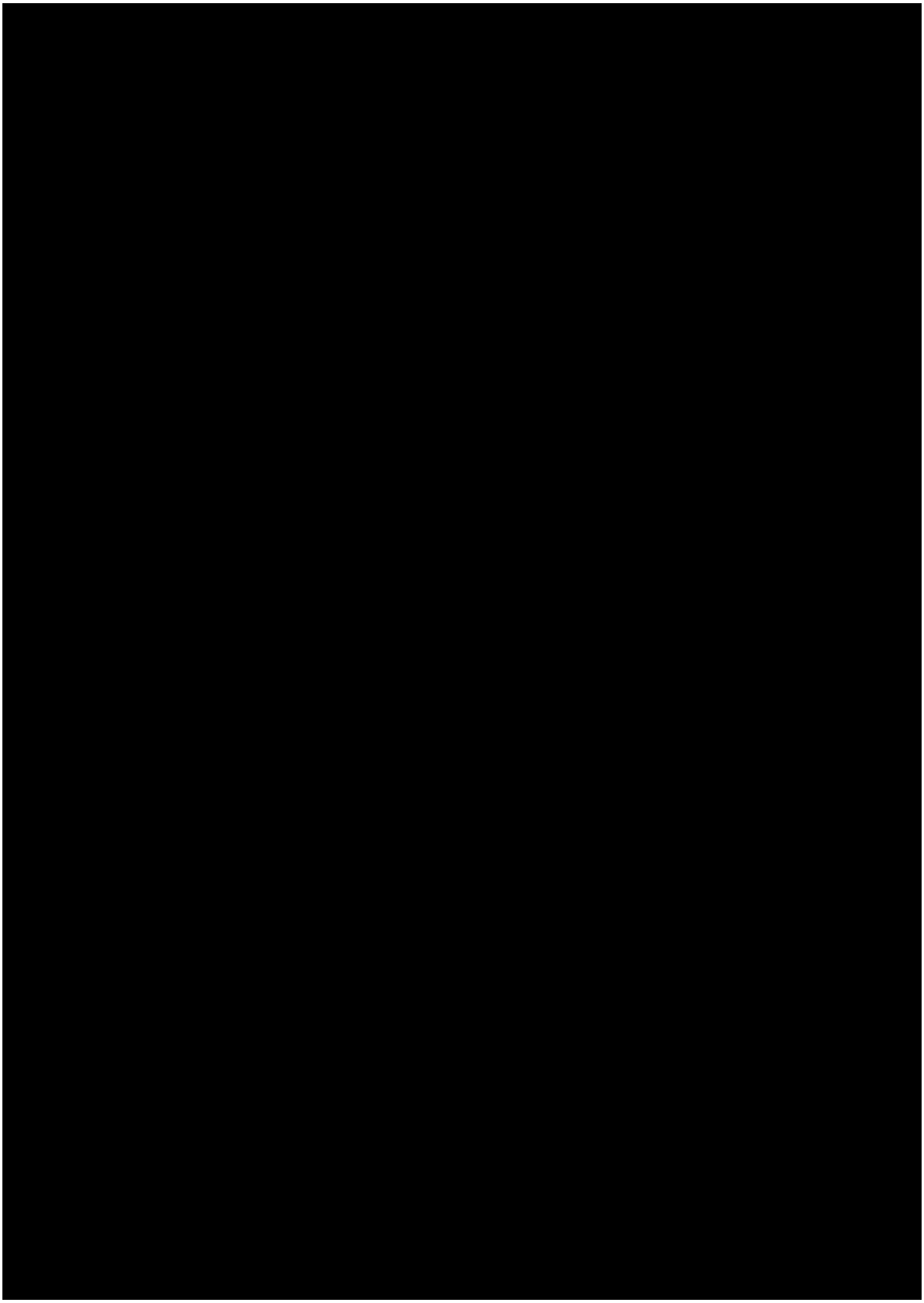
10.10. Appendix 10: Lansky Performance Status (for use in subjects <16 years old)

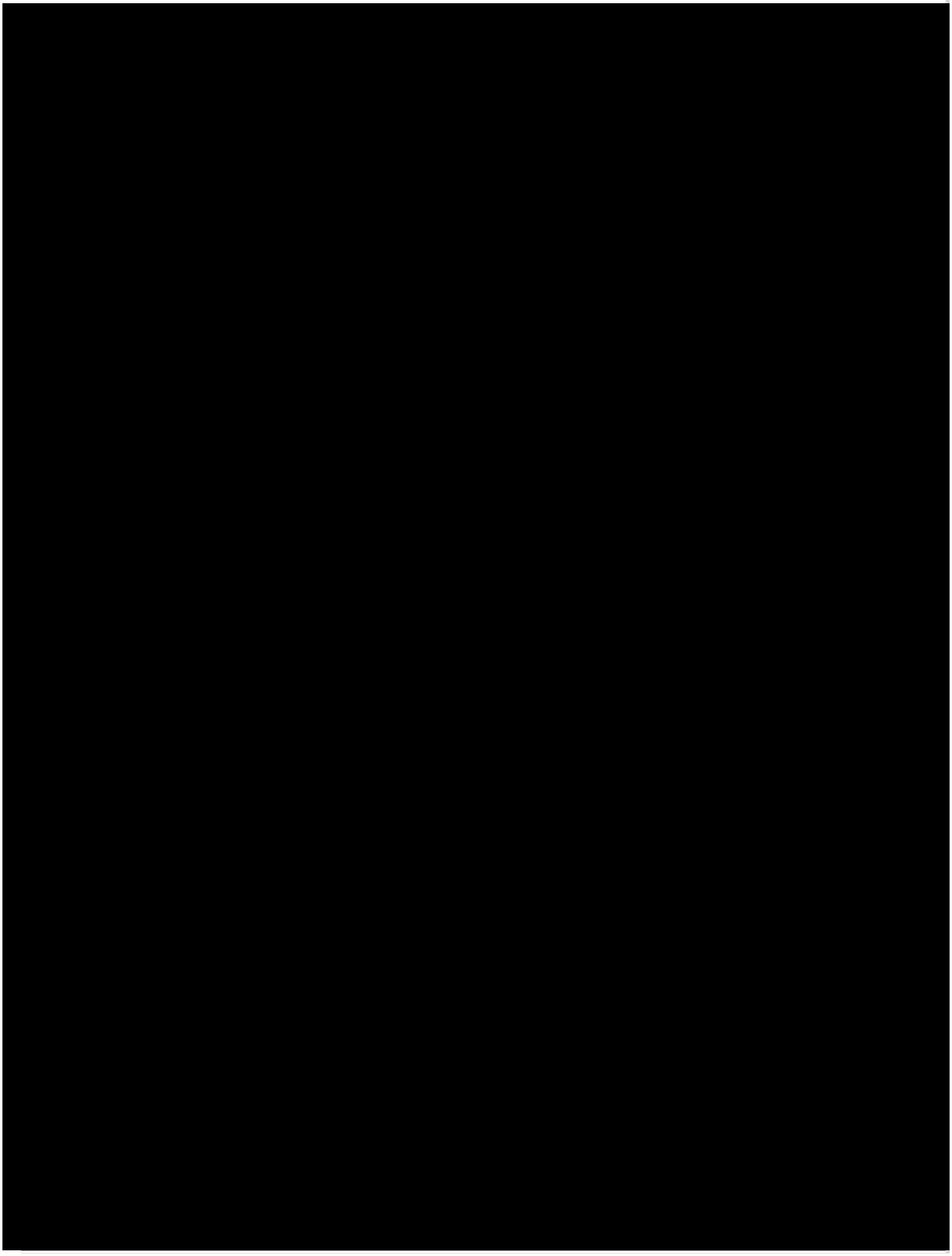
Mapping to ECOG	Lansky	
Score	Score	Description
0	100%	Fully active, normal.
	90%	Minor restrictions in physically strenuous activity.
1	80%	Active, but tires more quickly.
	70%	Both greater restriction of, and less time spent in, play activities.
2	60%	Up and around, but minimal active play; keeps busy with quieter activities.
	50%	Gets dressed, but lies around much of the day; no active play; able to participate in quiet play and activities.
3	40%	Mostly in bed; participates in quiet activities.
	30%	In bed; needs assistance even for quiet play.
4	20%	Often sleeping; play entirely limited to very passive activities.
	10%	No play; does not get out of bed
5	0%	Unresponsive; Dead

[Lansky, 1987]

10.11. Appendix 11: EQ-5D-3L Health Questionnaire (SAMPLE)

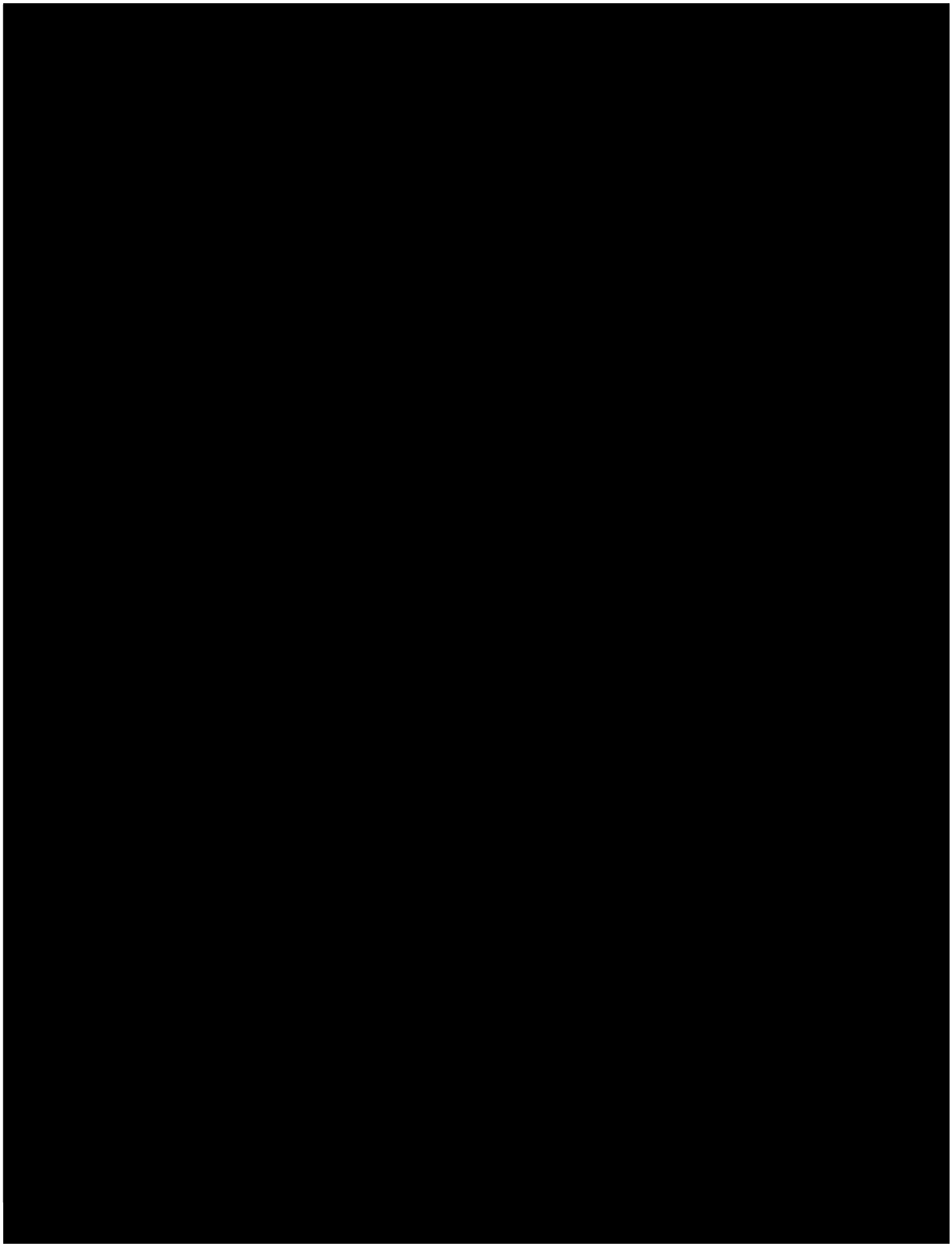




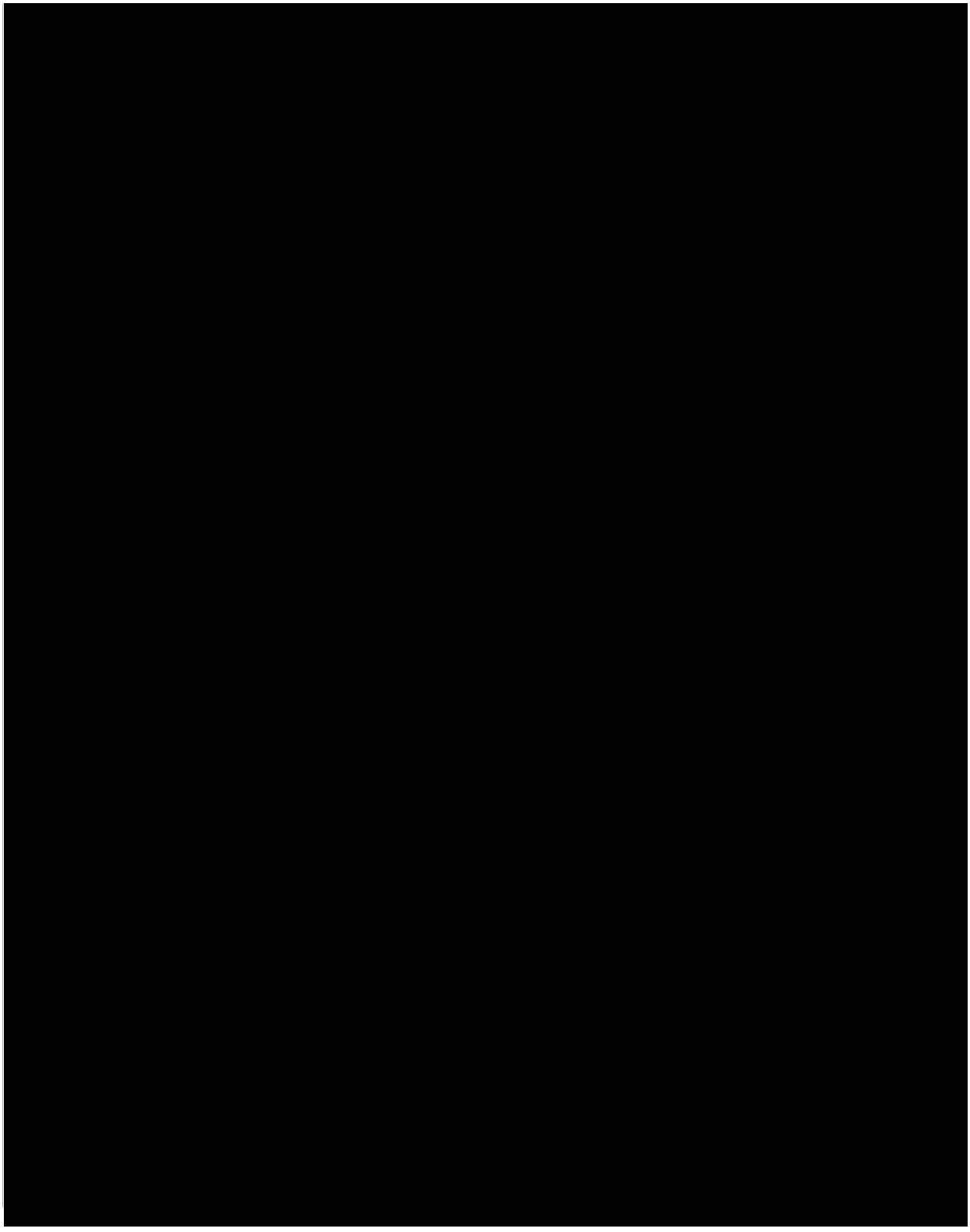


10.12. Appendix 12: EORTC-QLQ-C30 Questionnaire (SAMPLE)

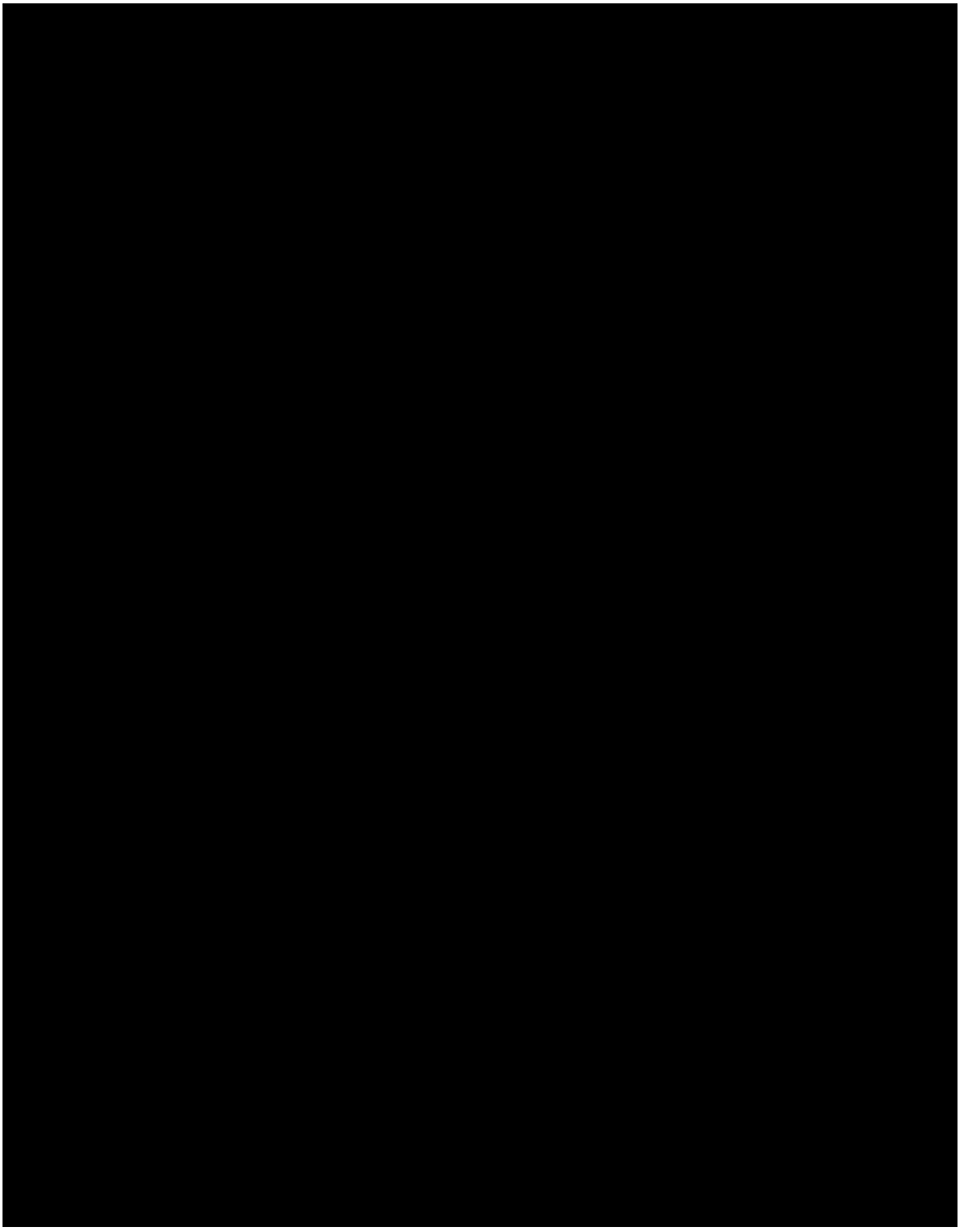
ENGLISH

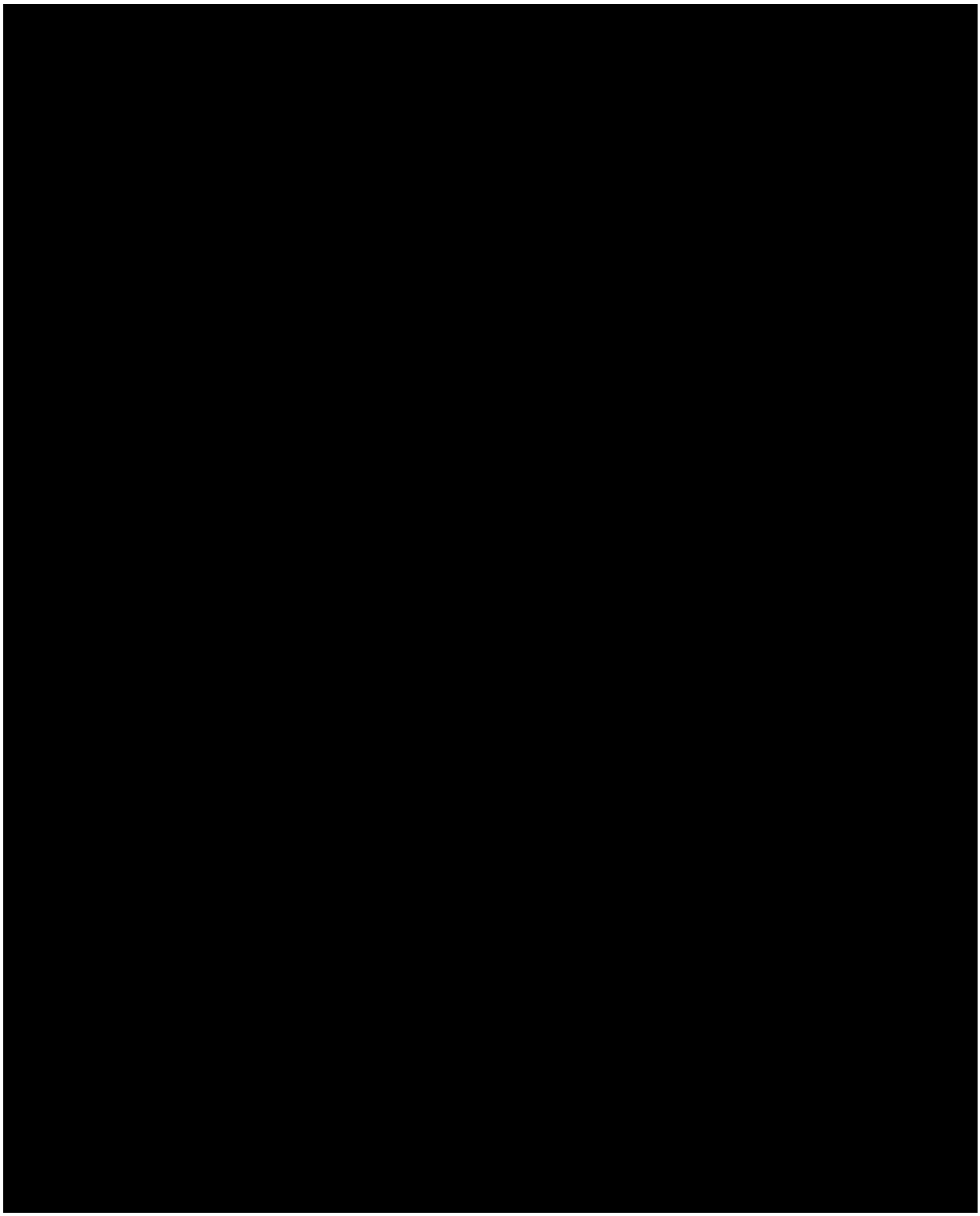


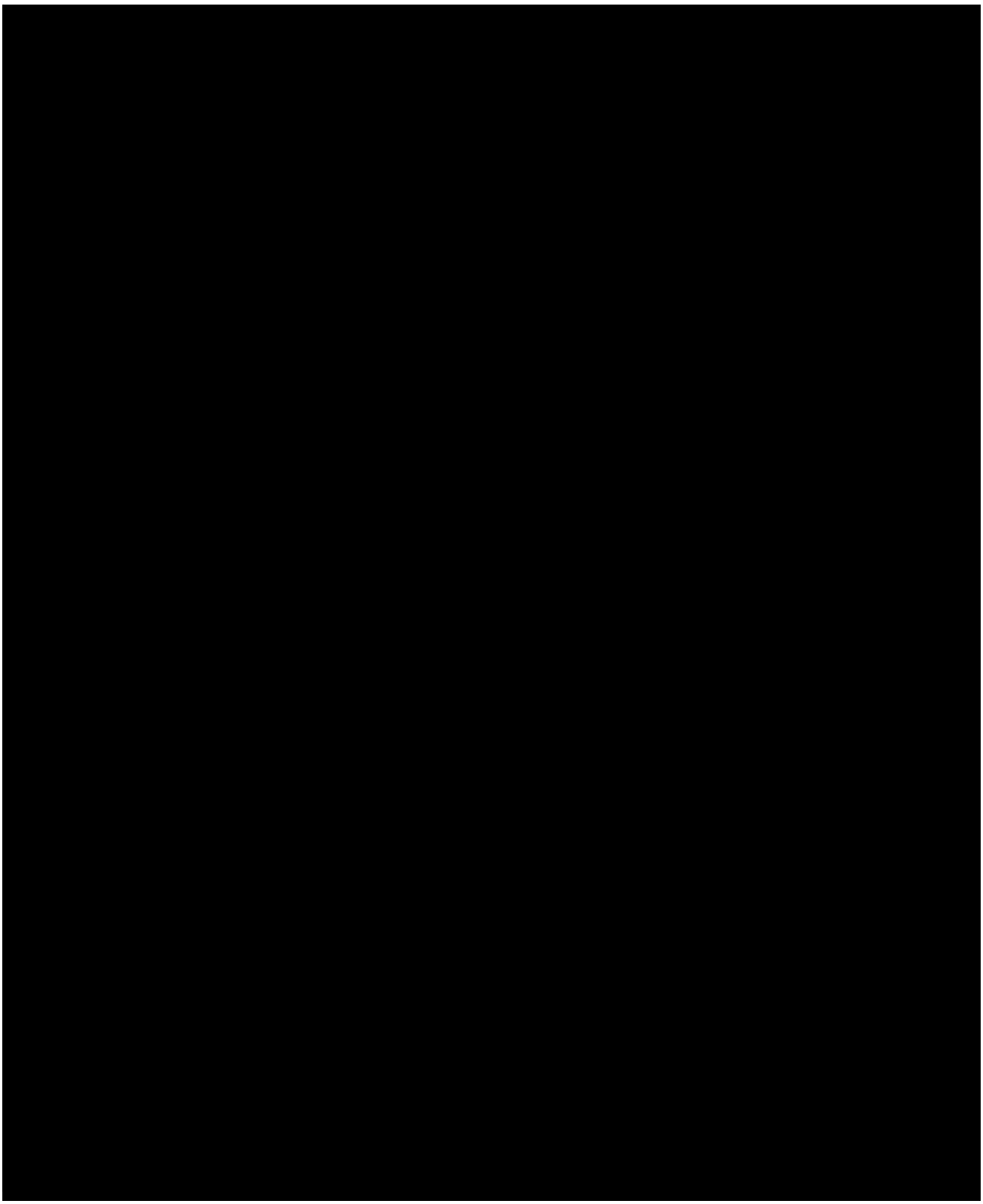
ENGLISH

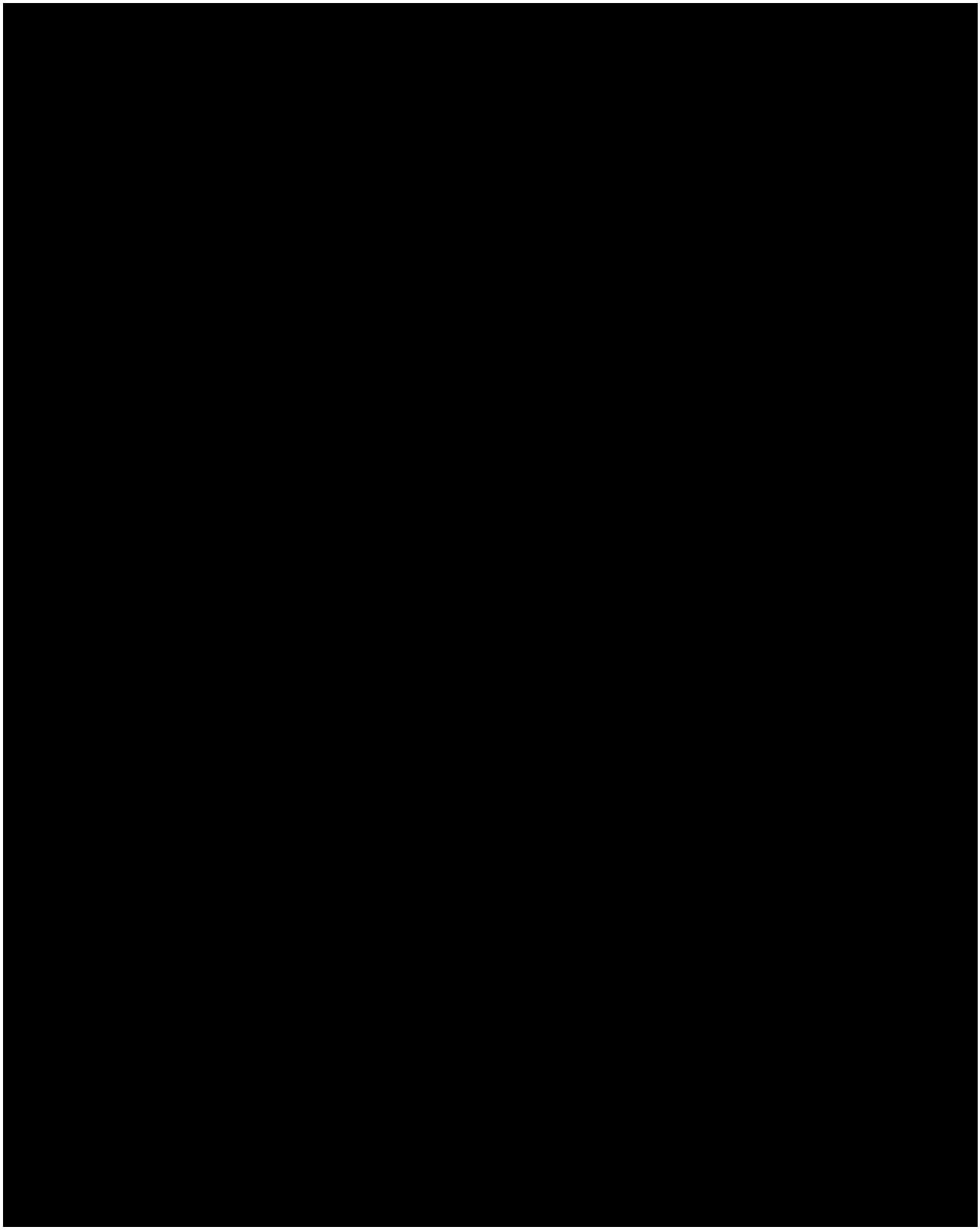


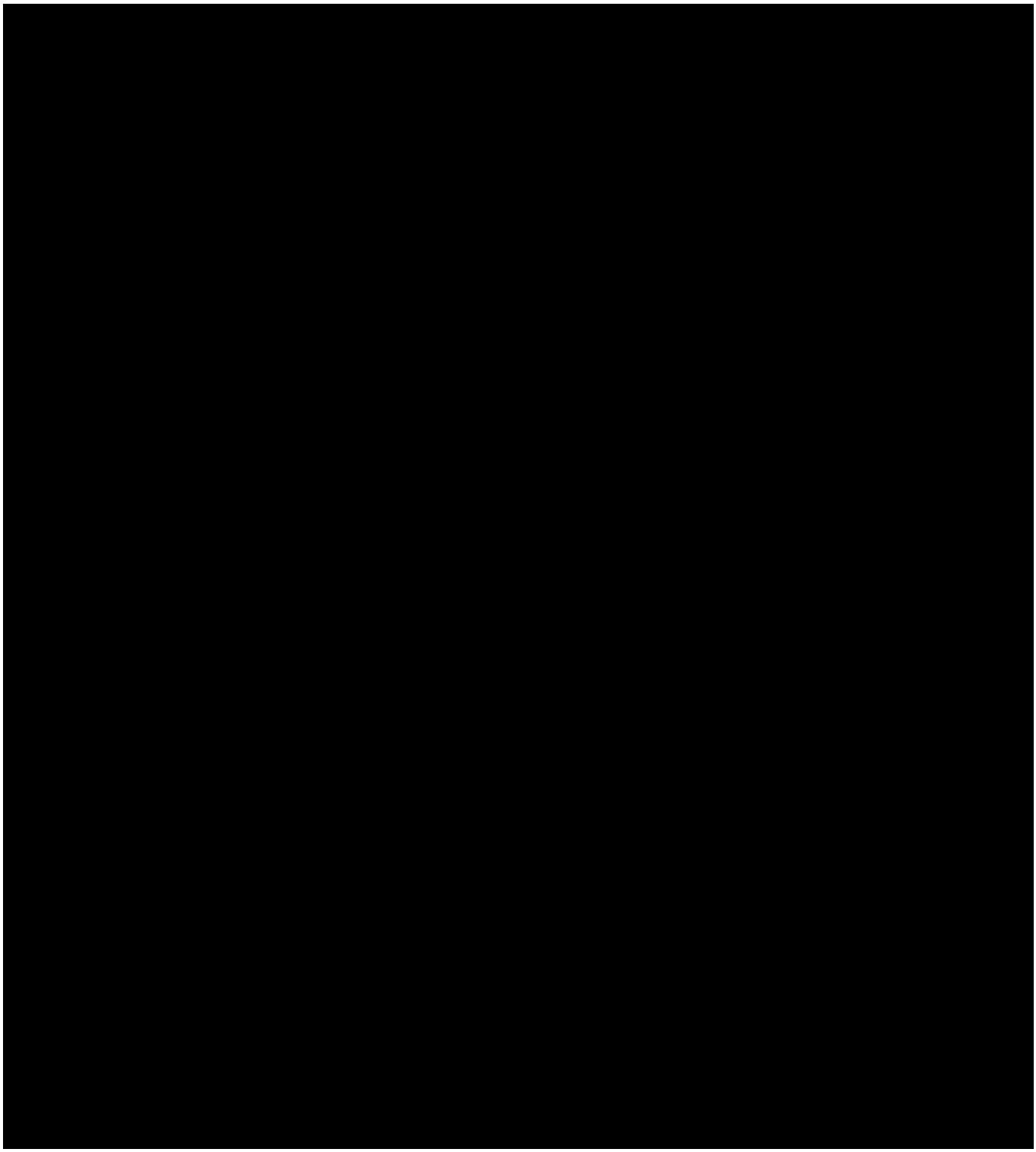
10.13. Appendix 13: PedsQL™ Questionnaire (SAMPLE)

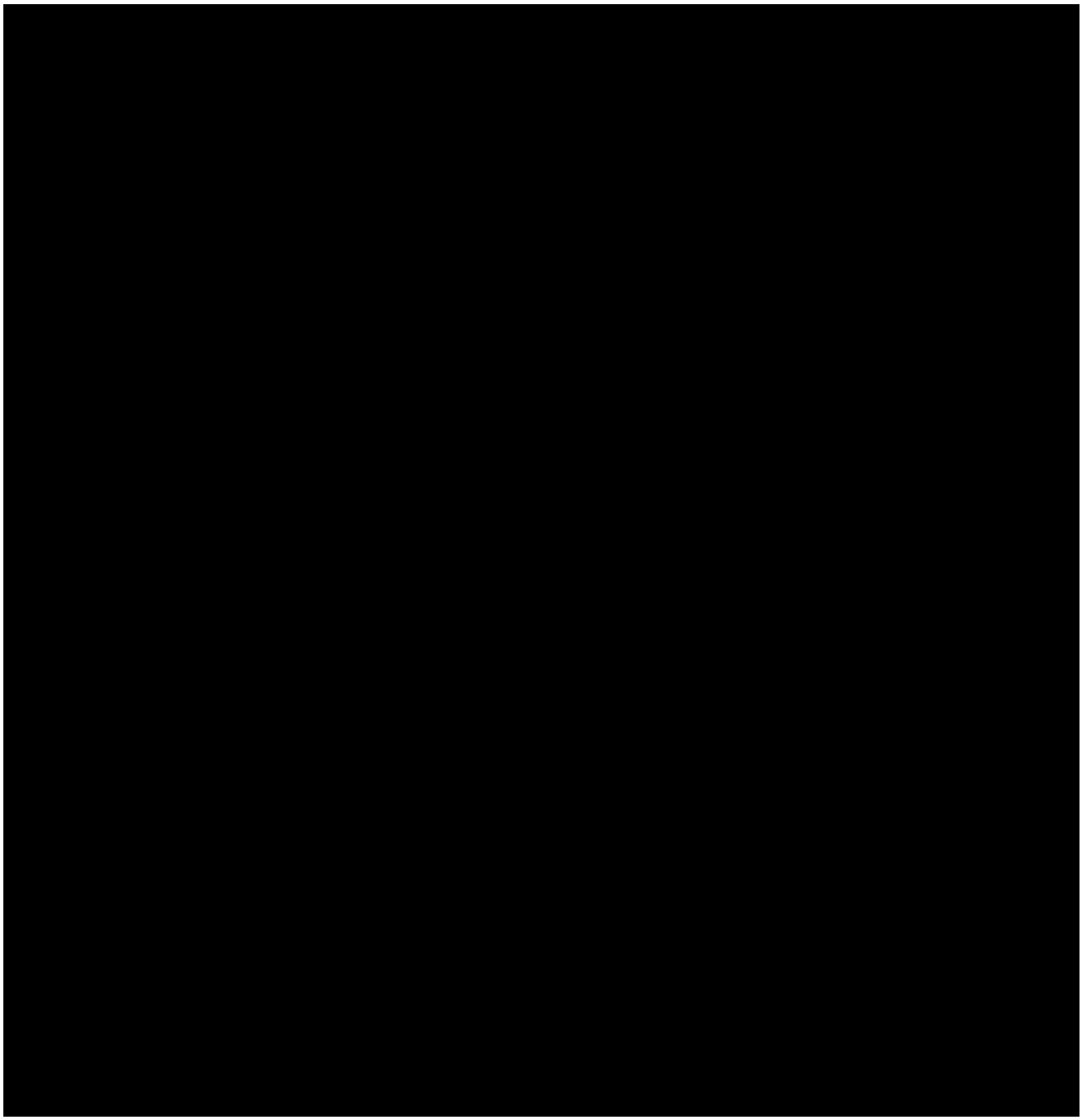


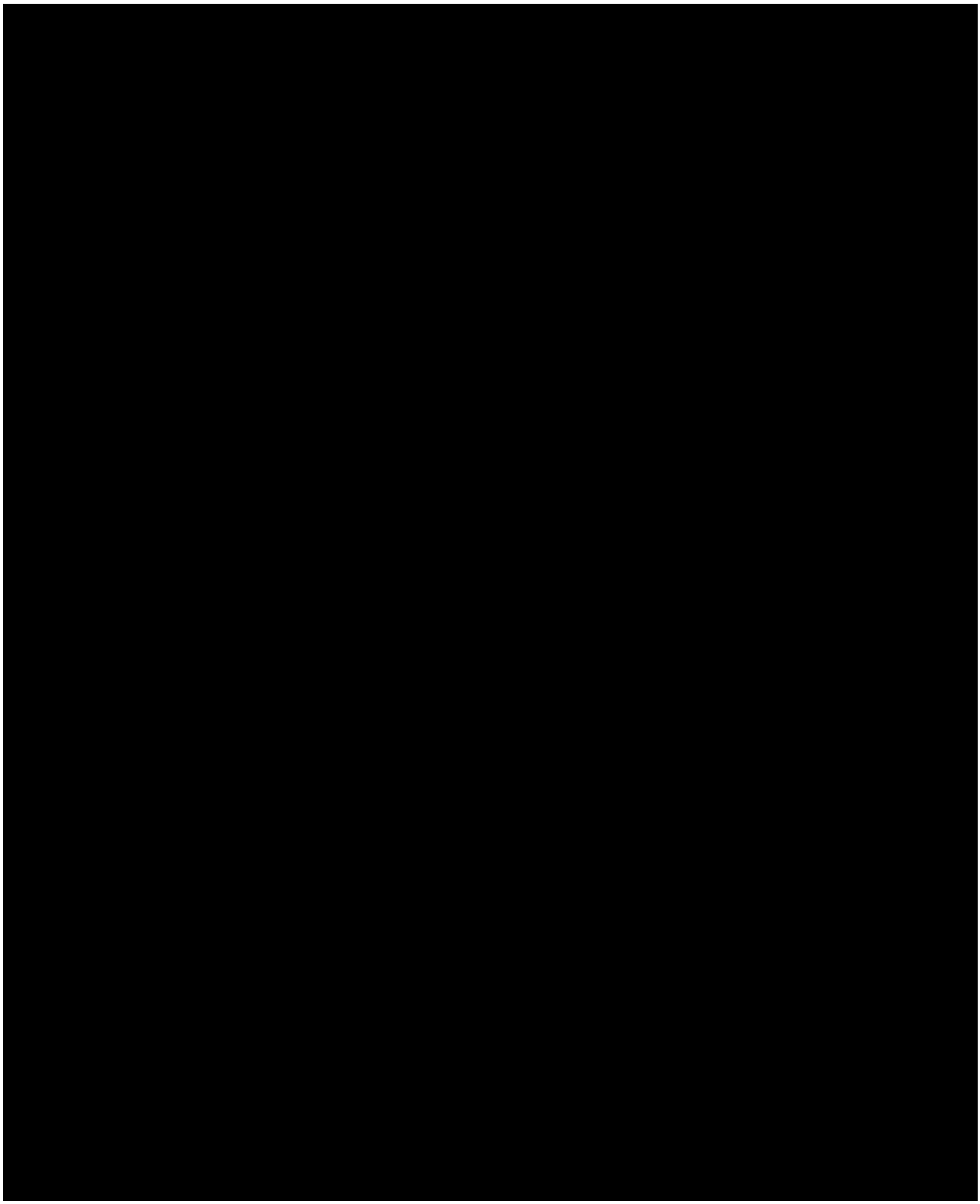


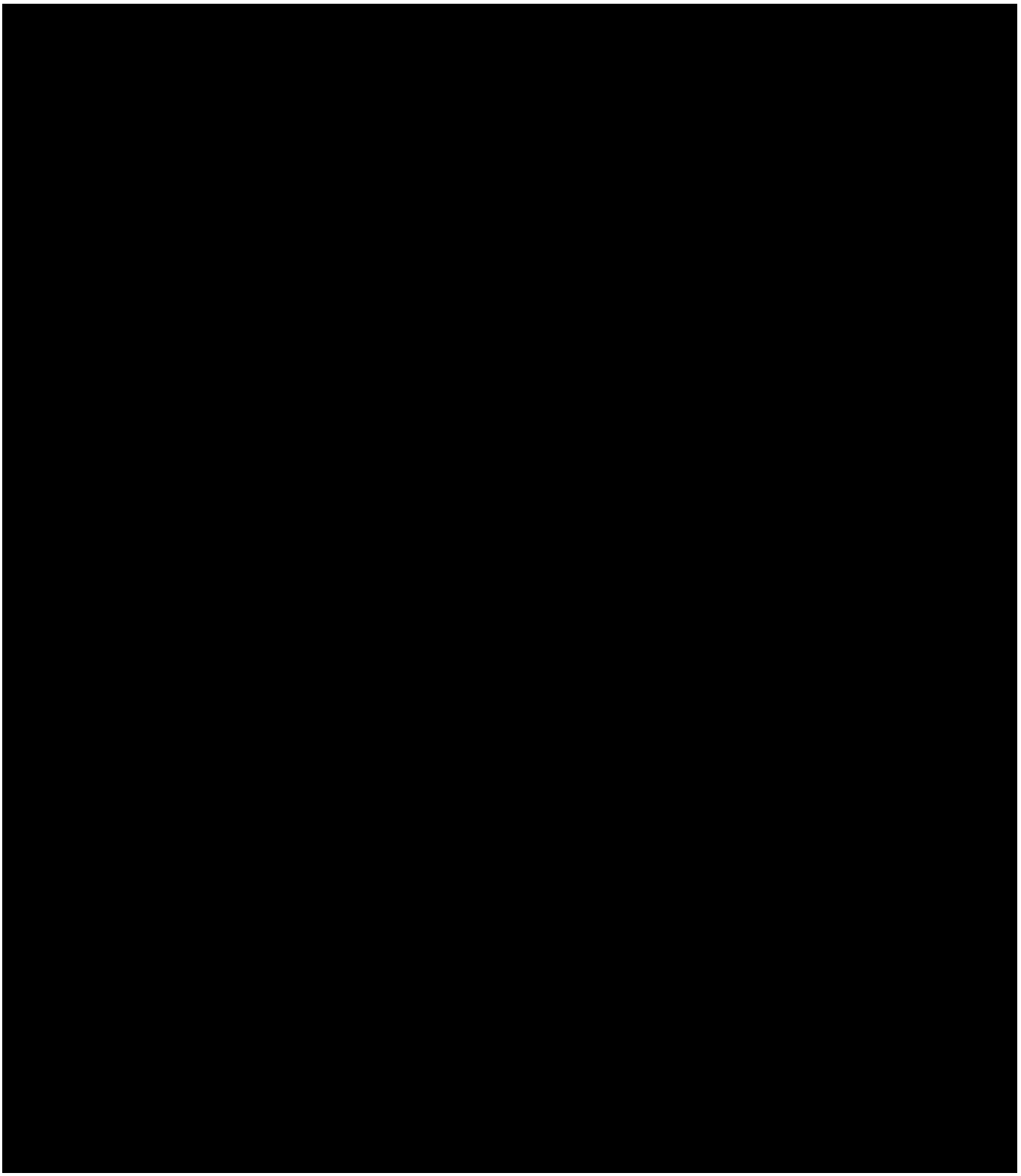


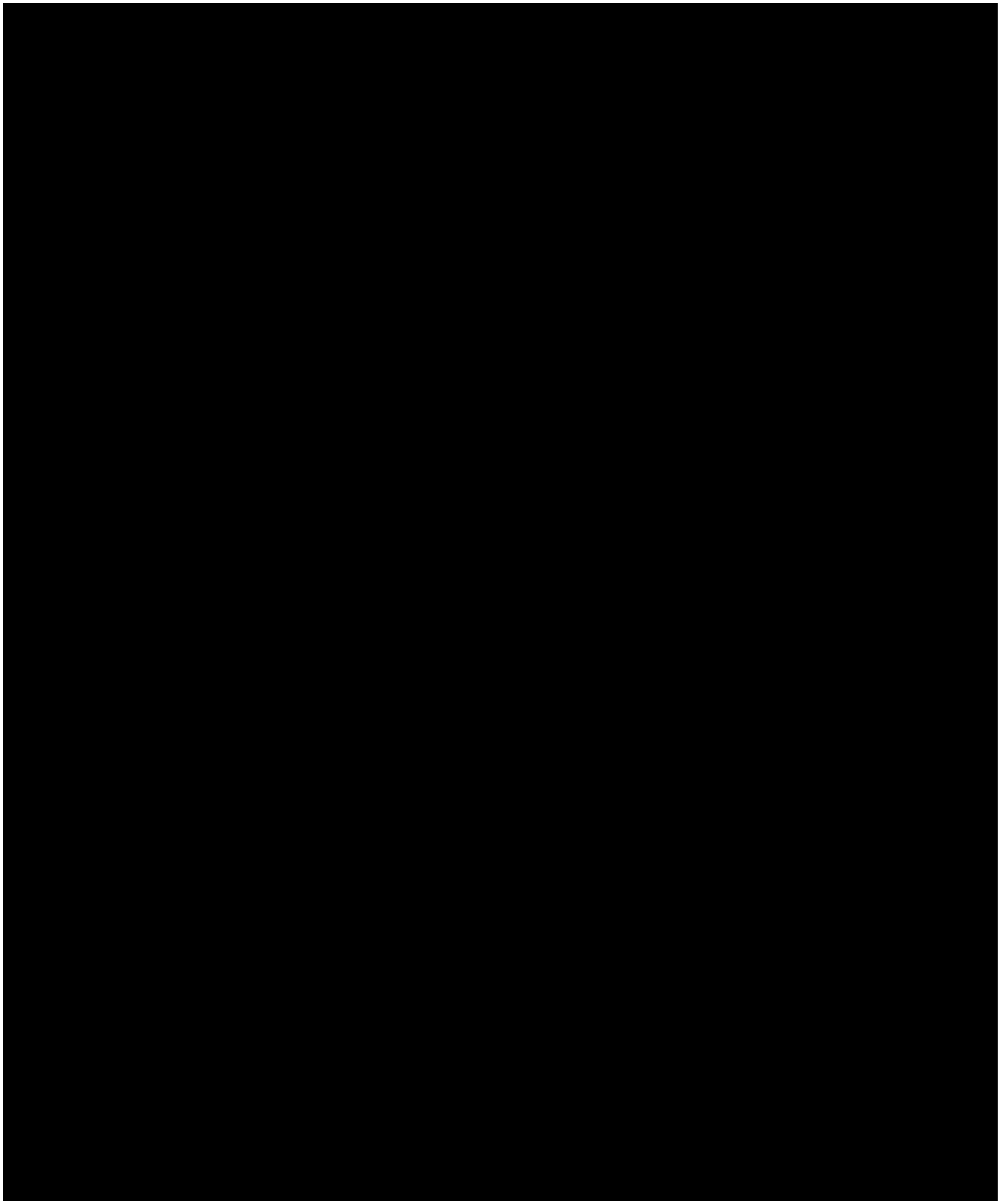


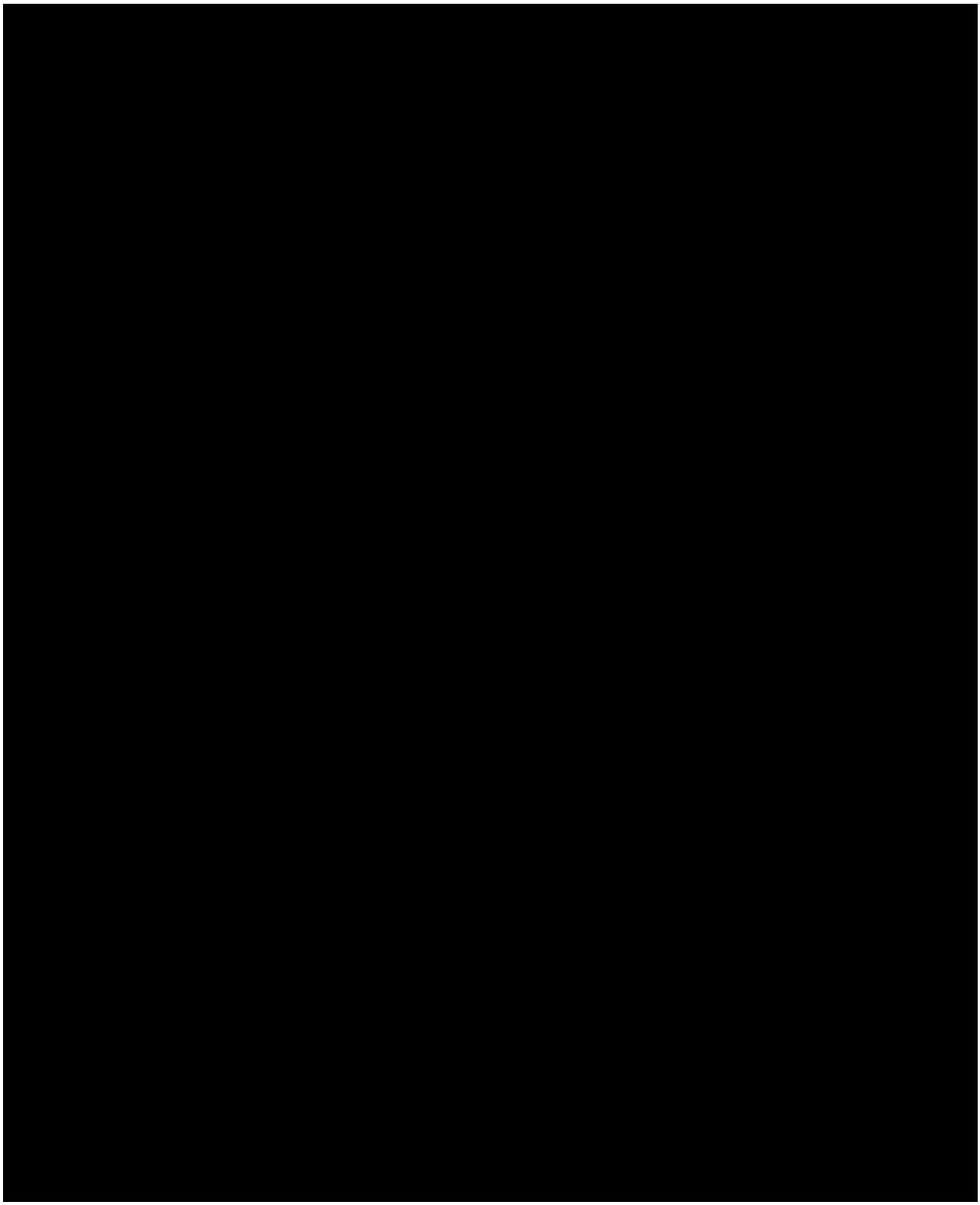


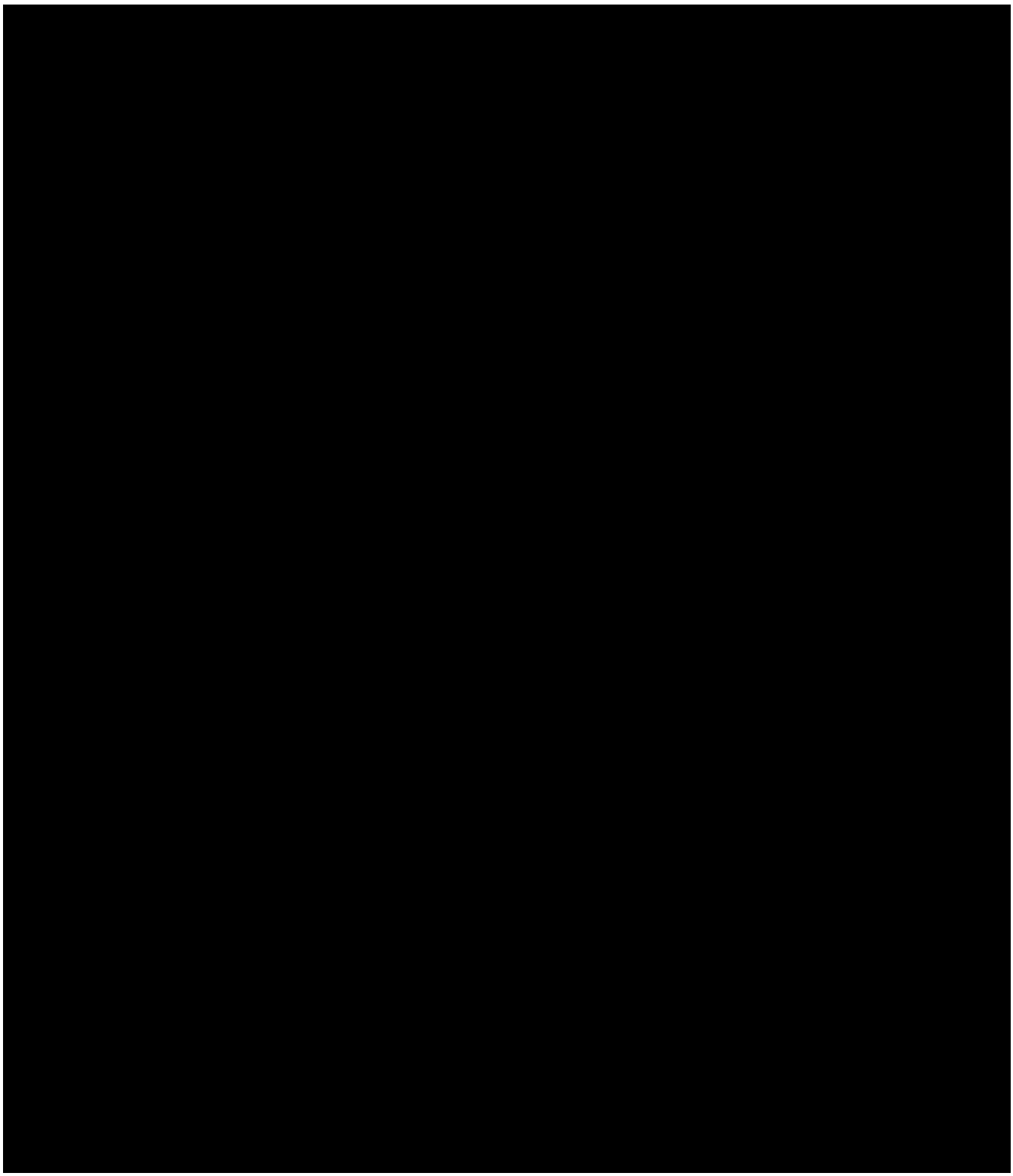


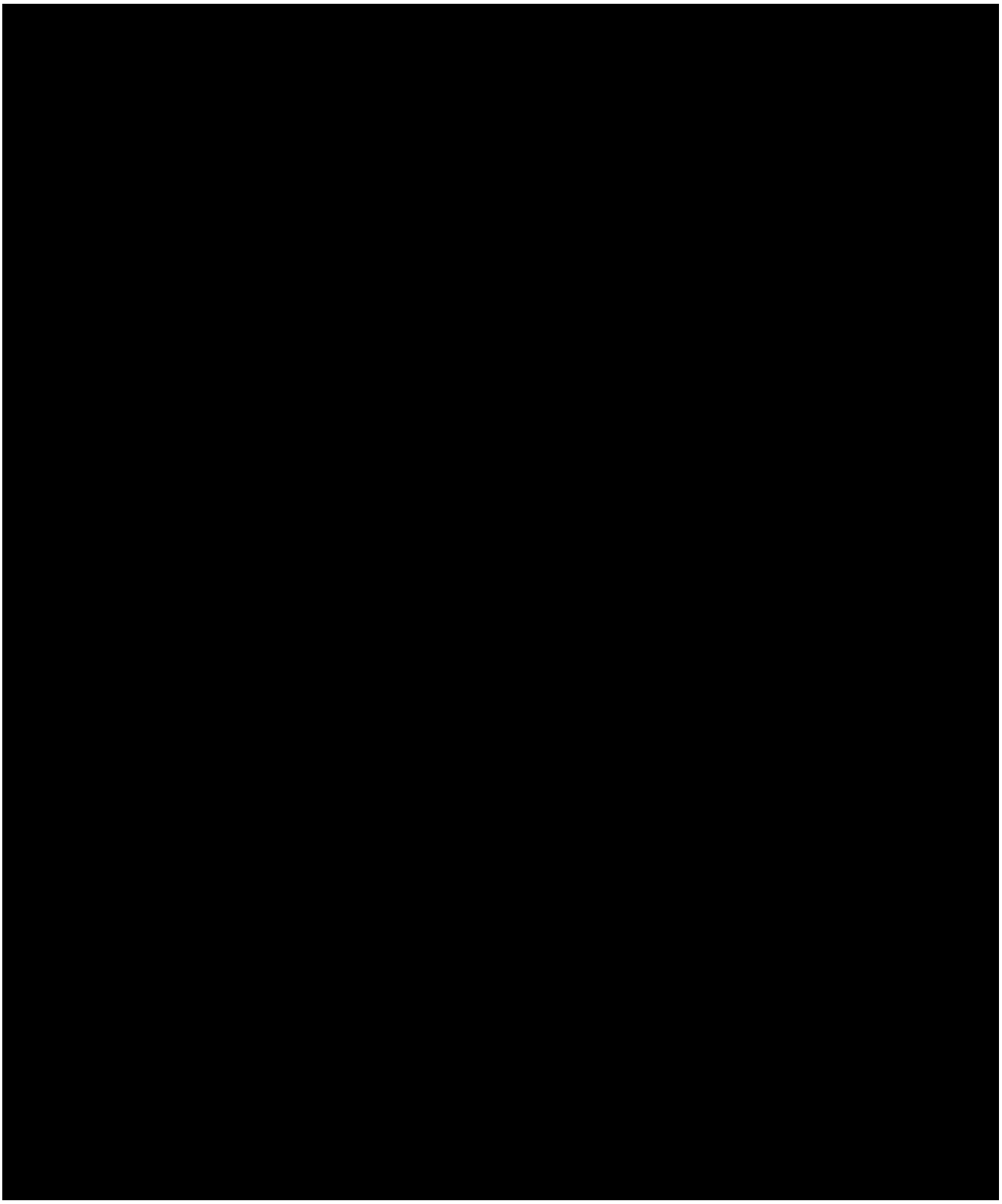












10.14. Appendix 14: Abbreviations

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

AE	Adverse event
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BOR	Best overall response
CAPD	Cornell Assessment Pediatric Delirium Score
CBC	Complete blood count
CDC	Centers for Disease Control
cfDNA	Cell free DNA
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete response
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CT	Computerized tomography
CTA	Cancer-testis antigen
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DoSD	Duration of stable disease
DSMB	Data Safety Monitoring Board
EBV	Epstein Barr virus

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

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

NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal Investigator
PTT	Partial thromboplastin time
PR	Partial response
qPCR	Quantitative polymerase chain reaction
RAC	Recombinant DNA Advisory Committee
RC	Research Committee
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
RIND	Reversible ischemic neurologic deficit
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
SCID-X	Severe combined immunodeficiency disease – X linked
SD	Stable disease
SGPT	Serum glutamate-pyruvate transaminase
SIN	Self-inactivating
SOP	Standard operating procedure
SPEAR	Specific Peptide Enhanced Affinity Receptor
SPM	Study Procedures Manual
SRC	Safety Review Committee
SUSAR	Suspected, unexpected serious adverse reactions
TCR	T cell receptors
TIA	Transient ischemic attack

TILs	Tumor-infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TTR	Time to response
TURBT	Transurethral resection of bladder tumor
ULN	Upper limit of normal
VSV-G	Vesicular Stomatitis Virus G glycoprotein
WBC	White blood cell
WHO	World Health Organization
X-CGD	X-linked chronic granulomatous disease

10.15. Appendix 15: Protocol Amendment History

Protocol Version Amendment 3, FR 4.0 (FR-4.0) dated 18MAY2021 is replaced in France only by Protocol Amendment 3, FR 5.0 (FR-5.0) dated 28OCT2021.

Sections amended	Change	Rationale for change
Time and Events 1.3 and section 8.7	Update to blood volume collection to comply with European recommendations for pediatric subjects	Addition requested by ANSM
Synopsis, 5.2	Inclusion criteria 5 updated to include progression within 6 months of the neoadjuvant/adjuvant treatment	Addition requested by ANSM
Synopsis, 5.2	Inclusion Criteria 9 updated to include Lansky score ≥ 80%	Addition requested by ANSM
10.2.2	Inclusion of SRC	Addition of SRC to ensure safety oversight of pediatric subjects as requested by ANSM

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