Protocol Number GSK208749 (ADP-0011-004)

A Pilot Open-Label Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC)

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: A Pilot Open-Label Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC)

I, the undersigned, have reviewed the protocol, including the appendices, and I will conduct the clinical study as described and will adhere to International Conference on Harmonization (ICH) tripartite guideline E6 (R1): Guideline for Good Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the NY-ESO-1^{c259}T Investigator Brochure.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: A Pilot Open-Label Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC).

Product Name: NY-ESO-1^{c259}T

Protocol Number: GSK208749 (ADP-0011-004)

IND Number: 14603

EudraCT Number: 2016-002517-21

Date of Original Protocol: 08-June-2015

Amendment Number	Date	Reason for Change
01	08-August-2016	This amendment was performed to address questions and comments from Institutional Review Boards and Regulatory Authorities. Additionally, revisions were made based on emerging data from Adaptimmune's clinical program and due to Adaptimmune's newly developed protocol template. Appendix 7 contains a summary of and rationale for all revisions for Amendment 01. Key revisions included the following: Changed phase of trial from Phase I/II to Pilot Revised Background and Study Rationale sections to minimize information already provided in the NY-ESO-1^{c259}T Investigator Brochure Revised primary, secondary, and exploratory endpoints to better characterize the safety and efficacy evaluations, and correlative studies to be performed in this study Changed lymphodepleting chemotherapy regimen from cyclophosphamide alone to cyclophosphamide and fludarabine based on emerging data from our ongoing clinical program Removed human leukocyte antigen (HLA) and antigen expression screening since these tests will be performed in Adaptimmune's Screening Protocol (ADP-0000-001) Revised inclusion/exclusion criteria to provide more clarity on subject population Added guidance on second T cell infusion, including eligibility criteria and Schedule of Procedures table

		Added text around the administration of cyclophosphamide and fludarabine, including dose adjustments, prophylactic and supportive treatments Removed immune-related Response Criteria (irRC) criteria for tumor response assessments Added several sections on supportive care guidance, including infection, hematologic and blood product support, autoimmunity, GVHD, and pancytopenia
02	16-July-2017	Subsequent to the licensing of Adaptimmune product NY-ESO by GSK, the purpose of this protocol amendment is to: - Delete or replace references to Adaptimmune or its staff with that of GlaxoSmithKline (GSK) and its authorized agents to align with the change of sponsorship; - Make administrative changes to align with GSK processes and procedures; - Update language relating to serious adverse event (SAE) reporting and safety monitoring; - Changes to lymphodepletion regimen throughout. Appendix 7 contains a summary of revisions for Amendment 02.
03	17-October-2018	Changes made to the protocol were requested by the FDA as a result of safety events which included 2 reports of Guillain-Barré syndrome in subjects who have received chemotherapy and GSK3377794 during clinical trials.

Amendment 4

Overall Rationale for the Amendment:
The overall rationale for this amendment is to clarify patient management with regards to treatment regimen and evaluation of encephalopathy and modification of lymphodepleting regimen for older participants, modification of target dose range for NY-ESO transduced cells and changes related to Health Canada requests including updates to both the Encephalopathy (now Immune Effector Cell-Associated Neurotoxicity or ICANS) and the CRS grading and management criteria.

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 3.1-Overall Study Design Section 3.2.5-Rationale for NY-ESO-1c259 T Cell Dose	Removed the target dose and modify range to 1 to 8 x10^9 transduced cells.	To align with other protocols across the GSK3377794 program and to improve protocol clarity
Section 3.1 Figure 1	Updated figure to remove weeks 3, 5, 6, and 10	Changes were made to be consistent with changes in Table 15 in the protocol
Section 3.5.1-Benefit Assessment Section 3.5.2 -Risk Assessment	Made changes to update safety profile for GSK3377794 based on GSK3377794 Investigator's Brochure 2019	Changes were made to align with GSK3377794 Investigator's Brochure 2019
Section 4.7 Consideration for Temporary Suspension of Enrollment	Revised Study stopping and pausing rules	To align with other protocols across the GSK3377794 program
Section 3.2.3 Section 5.2 Lymphodepleting Therapy	Added option to revise lymphodepleting therapy for participants with documented history of severe and prolonged cytopenia	To improve participants safety
Section 3.2.3 Section 5.2 Table 2 Section 5.2.1 Lymphodepletion Dose Modification	Added lymphodepleting regimen adjustments for participants ≥60 years old and participants with severe cytopenia	To improve participants safety
Section 7.2 Table 4 and 5 and Appendix 5 Table 15 - Schedule of Activities (SoA)	Revised to include changes from CARTOX to ICE and clarify the collection of liquid biopsy samples.	Changes were made to be consistent with changes in the text in the protocol and to align with other protocols across the GSK3377794 program
Section 7.2 Schedule of Procedures Table 4 (Interventional Phase 1)	Added blood collection for cytokine analyses	This cytokine sample is being included to determine a cytokine profile at time of biopsy & will also serve as 'baseline' cytokine level, prior to lymphodepletion for the 2nd infusion.

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Schedule of Procedures Table 5 (Long Term Follow-up)	Revised text to be consistent with text in Section 7.2, including collection of delayed AEs.	To be consistent with changes elsewhere in this section
Section 7.4.8 Long Term Follow-up	Clarified when delayed AEs would be collected	To align with other protocols across the GSK3377794 program To improve protocol clarity and safety monitoring
Section 8.5 Management of Cytokine Release Syndrome (CRS)	Revised guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system [Lee, 2019]	Changes were based on Regulatory Agency feedback
8.9 Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) And Table 11	Revised guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system [Lee, 2019]	Changes were based on Regulatory Agency feedback
Section 8.10- Management of Guillain-Barré Syndrome (GBS)	Added language to utilize diagnostic guidance for GBS [Fokke, 2014; Walgaard 2010; Walgaard 2011]	To align with other protocols across the GSK3377794 program To improve protocol clarity and safety monitoring
9.1 Time Period for Collecting AE and SAE Information	Added clarification to AEs collected during the various timepoints of the study	To improve protocol clarity
9.4 Reporting Criteria During Long-Term Follow-Up (Years 1 - 15)	Added clarification to AEs collected during the various timepoints of the study	To improve protocol clarity
Section 10.2 Mandated Study Pause Due to GBS	Revised language to utilize diagnostic guidance for GBS [Fokke, 2014]	To align with other protocols across the GSK3377794 program

Section # and Name	Description of Change	Brief Rationale
Section 11.3 Study Populations	Removed text regarding leukapheresis date from the definition of the ITT population	To align with other protocols across the GSK3377794 NSCLC program
Appendix 5, Table 15 Schedule of Procedures	Removed Week 3, 5, 6, and 10 visits from the 2nd Infusion Schedule of Procedures. Added collection of liquid biopsies at D1, D8, W4 and W16. Samples to evaluate persistence for research were added at Baseline and Week 16 and Week 12 sample	The evaluations atWeeks 3, 5,6, and 10 are no needed based on prior experience in patients treated with t-cell infusions on this study. Persistence samples were added at Baseline and Week 16 to correlate to second, confirmatory imaging and a sample at Week 12 sample for consistency with the first infusion table

CONFIDENTIALITY STATEMENT

DECLARATION

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

RESPONSIBLE SPONSOR STUDY PHYSICIAN/SPONSOR INFORMATION PAGE

Sponsor Signatory

PPD

25-SEP-2019

Benedetto Farsaci,
Medical Director,
GlaxoSmithKline

Date

Sponsor Details

1250 South Collegeville Road,
Collegeville,
PA 19426-0989

PPD

SYNOPSIS

Title: A Pilot Open-Label Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Subjects with Stage IIIb or Stage IV Non-Small Cell Lung Cancer (NSCLC).	
Short Title	NY-ESO-1^{c259}T for advanced NSCLC
Protocol Number	GSK208749 (ADP-0011-004)
Phase	Pilot
Methodology	This is an open-label clinical trial in subjects with locally advanced or metastatic NSCLC. Subjects with the HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 allele, whose tumor expresses the NY-ESO-1 and/or L antigen family member-1a (LAGE-1a) tumor antigen, and who meet study entry criteria will be eligible to receive autologous genetically modified T-cells (NY-ESO-1^{c259}T). The trial is conducted with outpatient procedures; however, subjects may be hospitalized for the lymphodepleting chemotherapy at the discretion of the Investigator. It is recommended that the T cell infusion is an inpatient procedure to allow for close monitoring of post-infusion adverse events. Upon enrollment, subjects will undergo leukapheresis for T cell collection, and their cells will be genetically engineered and expanded ex vivo. The manufacturing of T cells will take approximately 28 days. Prior to receiving T cells, subjects will undergo lymphodepleting chemotherapy with cyclophosphamide and fludarabine on Day -7, Day -6, and Day – 5 followed by the cell infusion on Day 1. Safety and tolerability as well as anti-tumor activity and biomarker assessments to be conducted at each visit are outlined in the Schedule of Procedures. Tumor response will be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 by Investigators and scans will be collected and stored at a central imaging laboratory for possible independent review. Tumor biopsies for research studies will be taken at Baseline, Week 8 and upon progression of disease. Subjects who have a confirmed response (or have stable disease for >4 months) but subsequent disease progression following the initial infusion and whose tumor continues to express the appropriate antigen target may be eligible for a second infusion. All subjects, completing or withdrawing from the Interventional Phase of the study, will enter a 15-year long-term follow-up phase for observation of delayed adverse events in accordance

	with Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements for gene therapy clinical trials. All subjects will continue to be followed for overall survival during the long-term follow-up phase.
Study Duration	It is anticipated that this trial will take approximately 18-24 months to enroll, with the study completion approximately 24-30 months after initiation (approximately 6 months after the last subject is enrolled). Patients will be followed in the long-term follow-up (LTFU) protocol for up to 15 years.
Study Center(s)	This is a multi-center study, including approximately 15 sites in North America and Europe. Additional sites may be added at the discretion of the Sponsor.
Number of subjects	10 subjects

Objectives	**Endpoints**
Primary: To evaluate the safety and tolerability of autologous genetically modified T cells (NY-ESO-1^{c259}T) in human leukocyte antigen (HLA) HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive subjects with NY-ESO-1 and/or LAGE-1a positive advanced NSCLC.	Adverse events (AE), including serious adverse events (SAE); Change of laboratory assessments, including chemistry, hematology, and coagulation; Cardiac and pulmonary assessments, including electrocardiogram (ECG) and pulmonary function (pulse oximetry).
Secondary: To evaluate the efficacy of NY-ESO-1^{c259}T	Overall Response Rate (ORR) per RECIST 1.1 Time to response Duration of response Disease Control Rate (DCR) Progression-free Survival (PFS)
Exploratory: To evaluate the persistence, phenotype and functionality of NY-ESO-1^{c259}T	Correlate persistence, phenotype and functionality of NY-ESO-1^{c259}T in the peripheral blood and/or tumor with response to treatment Correlate circulating cytokines with cytokine release syndrome (CRS)

Exploratory: To understand mechanisms of resistance to NY-ESO-1^{c259}T	Correlate changes in immunosuppressive myeloid cells and Tregs in peripheral blood versus tumor Correlate changes in immunosuppressive myeloid cells and Tregs in peripheral blood and tumor with treatment response Investigate the immune contexture of each subjects' tumor over time and to understand mechanisms of tumor resistance, escape and treatment response Determine whether loss of NY-ESO-1^{c259}T expression in tumor is a resistance mechanism
Exploratory: To document the exposure and immunogenicity with NY-ESO-1^{c259}T	Change of anti-NY-ESO-1^{c259}T antibodies
Exploratory: To evaluate antigen spreading as a mechanism of response	Correlate clonal outgrowth of T cell populations with response following T cell infusion
Exploratory: To evaluate the survival benefit of NY-ESO-1^{c259}T	Overall Survival (OS)
Exploratory: To evaluate the efficacy of NY-ESO-1^{c259}T per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)	Overall Response Rate (ORR) per irRECIST Time to response (irRECIST) Duration of response (irRECIST) Progression-free Survival (PFS, irRECIST)
Key Inclusion /Exclusion Criteria	Key eligibility include: • Subject has histologically or cytologically confirmed diagnosis of advanced non-small cell lung cancer (stage IIIB or IV) or recurrent disease. • Subject has failed at least one platinum-containing regimen and have disease progression. Subjects with known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase receptor (ALK) or ROS1 gene rearrangements must have also received failed prior EGFR or ALK or ROS1 tyrosine kinase inhibitor,respectively (progressive disease [PD] or unacceptable toxicity). Subject

	may have received PD-1 or PDL-1 inhibitors. There is no limit on lines of prior anti-cancer therapy. • Subject has measurable disease according to RECIST v1.1 criteria. • Subject is HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive. • Subject's tumor (either an archival specimen or a fresh biopsy if archival tissue is unavailable) has been pathologically reviewed by a designated central laboratory confirming NY-ESO-1 and/or LAGE-1a expression. • Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 and anticipated life expectancy >3 months. • Subjects with a history of chronic or recurrent (within the last year prior to enrollment) severe autoimmune or active immune-mediated disease requiring steroids or other immunosuppressive treatments are NOT eligible. • Prior or active demyelinating disease Refer to protocol Section 4 for complete subject eligibility criteria for study entry.
Investigational Product, Dose, Route, Regimen	The product in this protocol is NY-ESO-1^{c259}T (an autologous genetically modified T-cell product) and will be manufactured at a central manufacturing site. Approximately 10 subjects will receive at least 1 x 10^9 transduced cells and a maximum of 8 x 10^9 transduced cells. In the event the minimum cell dose (1 x 10^9 transduced cells) cannot be achieved for a subject, that subject may be replaced with another subject. Up to two subjects may be replaced not to exceed a total of 12 subjects. A second infusion of NY-ESO-1^{c259}T cells may only be given to subjects who have documented progression of disease following an initial response and whose tumor continues to express the appropriate antigen target.
Comparator therapy	None
Statistical Methodology	Descriptive statistics will be provided for selected demographic, safety, response and correlative assessments as outlined in the statistical analysis plan. Descriptive statistics on continuous data will include the mean, median, standard deviation, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

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1 BACKGROUND AND RATIONALE

1.1 Non-Small Cell Lung Cancer

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

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

For early stage NSCLC, surgery is the treatment of choice; however, subsequent relapse at distant sites has resulted in the use of additional chemotherapy or radiotherapy. For subjects with advanced NSCLC that lack certain molecular alterations, such as ALK translocation or EGFR mutations, recommended first-line treatment is with platinum-based doublet chemotherapy. This generally consists of cisplatin or carboplatin with another cytotoxic agent (pemetrexed, taxanes, gemcitabine, vinorelbine or camptothecins). Other agents, such as bevacizumab or cetuximab, may be added to the regime. Erlotinib or afatinib may be indicated for subjects with sensitizing EGFR mutations or crizotinib or ceritinib in subjects with ALK rearrangements. In subjects who experience disease progression, single-agent chemotherapy or appropriate targeted drugs may be indicated as second- or third-line therapy. Furthermore, recent research into checkpoint inhibitors (e.g. anti-CTLA-4 and anti-PD-1 antibodies) have shown promising results in clinical trials with nivolumab, receiving marketing authorization in the US for treatment of advanced NSCLC who had received prior platinum-based chemotherapy.

1.2 Background to Adoptive T Cell Therapy

Adoptive T cell therapy (ACT) is a treatment that uses a cancer subject's own T lymphocytes with anti-tumor activity, expanded *in vitro* and re-infused into the subject. The ultimate objective of the process is the stimulation and expansion of potent and antigen-specific T cell immunity. There are numerous recent publications and reviews of ACT (Kalos, 2013; Klebanoff, 2016; Maus, 2014; Morgan, 2010; Robbins, 2011; Rosenberg, 2008).

The first observations that immune system engagement can lead to antitumor effects are often attributed to William Coley, who observed regression of sarcoma following severe bacterial infections in the 1890s. Further observations of the

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

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

Therefore, gene-transfer-based strategies have been developed to overcome the consequences of immune tolerance on the tumor-specific T cell repertoire. These approaches provide the potential to redirect T cells to effectively target tumors by the transfer of antigen-specific affinity-optimized T cell receptors. The majority of clinical approaches have employed T cells engineered to stably express transgenes via virus-based transduction. Virus-mediated gene transfer approaches typically employ vectors that are derived from gamma retroviruses or more recently lentiviruses.

Rational high-throughput genetic mutagenesis approaches have resulted in the ability to molecularly engineer TCRs with substantially higher affinities for target antigens. Affinity- enhanced TCR-based engineering approaches have certain inherent biological advantages, most notably that essentially all cellular proteins can be targeted because the approach is not limited to the targeting of cell surface epitopes, and the primary T cell activation signal is delivered in a physiological context, which may be relevant for optimal functionality of the infused T cells. Additional details are provided in the current NY-ESO-1^{c259} T Investigator Brochure.

1.3 Adoptive Immunotherapy with NY-ESO-1 Specific T Cells and Supporting data in NSCLC

Although progress has been made in the treatment of lung cancer, improvements have been modest leading to only 4% – 5% improvements in 5-year survival rates for disease Stages I – III and prolongation of only months for Stage IV (Johnson,

2014). In subjects with advanced NSCLC, new agent/ platinum combinations have generated overall response rates of approximately 25% – 35% which have plateaued. In addition, time to progression (4 – 6 months), median survival (8 – 10 months), 1 year survival rate (30% – 40%) and 2 year survival rate (10% – 15%) in fit subjects remain short.

However, NSCLC is now recognized as an immunologically targetable disease (Chow, 2013). Recent research into checkpoint inhibitors (e.g. anti-CTLA-4 and anti-PD-1 monoclonal antibodies) have shown promising results in clinical trials but have also demonstrated immune-related toxicities (skin, gastrointestinal, hepatic, endocrine and pneumonitis). Nivolumab received marketing authorization in the USA for treatment of subjects with advanced NSCLC who had received prior platinum-based chemotherapy (Bristol-Myers Squibb, 2016).

Published data indicates that NSCLC tumors express NY-ESO-1 (New York esophageal squamous cell carcinoma 1) with rates ranging approximately 11% to 43% of tumors (Grah, 2008; Gure, 2005). The Cancer Genome Atlas Ribonucleic acid (RNA) sequencing database indicates a frequency of expression of NY-ESO-1 in 12% in lung adenocarcinoma and 26% in squamous cell carcinoma and a frequency of expression of L antigen family member-1a (LAGE-1a) in 8.5% of adenocarcinoma and 21% of squamous cell (NCI, 2016).

1.4 Rationale for NY-ESO-1^{c259}T for NSCLC

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

1.4.1 Optimization of Lymphodepleting Chemotherapy Regimen

The most common lymphodepletion regimens used in ACT trials to date have incorporated cyclophosphamide or cyclophosphamide and fludarabine (Dudley, 2002; Dudley, 2005; Johnson, 2009; Robbins, 2011). The use of cyclophosphamide alone can achieve lymphodepletion without long-term immunosuppressive side effects. Therefore, in this study, cyclophosphamide alone was initially chosen for preconditioning.

Recent studies in lymphoma, chronic leukemia and acute leukemia using a chimeric antigen receptor (CAR) showed increased CD4+ and CD8+ CAR-T cell expansion, persistence and disease-free survival when fludarabine was added in to a previously cyclophosphamide-only preparative regimen (Turtle, 2016). The cyclophosphamide was administered at 30 – 60 mg/kg x 1 day and fludarabine at 25 mg/m^2/day x 3 – 5 days. Effective lymphodepletion has also been demonstrated in other CAR-T cell studies using reduced cyclophosphamide dosing than previously used, together with fludarabine (Batlevi, 2016). The lymphodepleting regimen in which objective tumor responses have been observed in an ongoing Adaptimmune clinical study in synovial sarcoma uses a cyclophosphamide dose of 1800 mg/m^2/day for 2 days, in addition to fludarabine 30 mg/m^2/day for 4 days (ClinicalTrials.gov Identifier: NCT01343043).

Based on the emerging data that the addition of fludarabine to cyclophosphamide may play a role in homeostatic expansion, the protocol has been amended to

evaluate cyclophosphamide and fludarabine as a lymphodepleting regimen. Refer to Section 3.2.3 for further rationale for lymphodepletion.

2 TRIAL OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of autologous genetically modified T cells (NY-ESO-1^{c259}T) in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive subjects with NY-ESO-1 and/or LAGE-1a positive advanced NSCLC	Adverse events (AE), including serious adverse events (SAE); Change of laboratory assessments, including chemistry, hematology, and coagulation; Cardiac and pulmonary assessments, including electrocardiogram (ECG) and pulmonary function (pulse oximetry).
Secondary	
To evaluate the efficacy of NY-ESO-1^{c259}T	Overall Response Rate (ORR) per RECIST 1.1 Time to response Duration of response Disease Control Rate (DCR) Progression-free Survival (PFS)
Exploratory	
To evaluate the persistence, phenotype and functionality of NY-ESO-1^{c259}T.	Correlate persistence, phenotype and functionality of NY-ESO-1^{c259}T in the peripheral blood and/or tumor with response to treatment Correlate circulating cytokines with cytokine release syndrome (CRS)
To understand mechanisms of resistance to NY-ESO-1^{c259}T	Correlate changes in immunosuppressive myeloid cells and Tregs in peripheral blood versus tumor Correlate changes in immunosuppressive myeloid cells and Tregs in peripheral blood and tumor with treatment response Investigate the immune contexture of each subjects' tumor over time and to understand mechanisms of tumor resistance, escape and treatment response Determine whether loss of NY-ESO-1^{c259}T or antigen expression in tumor is a resistance mechanism

To document the exposure and immunogenicity with NY-ESO-1^{c259}T	Change of anti-NY-ESO-1^{c259}T antibodies
To evaluate antigen spreading as a mechanism of response	Correlate clonal outgrowth of T cell populations with response following T cell infusion
To evaluate the survival benefit of NY-ESO-1^{c259}T	Overall Survival (OS)
To evaluate the efficacy of NY-ESO-1^{c259}T per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)	Overall Response Rate (ORR) per irRECIST Time to response (irRECIST) Duration of response (irRECIST) Progression-free Survival (PFS, irRECIST)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a pilot, open-label study of genetically engineered NY-ESO-1^{c259}T cells in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 subjects with advanced NSCLC. Approximately 10 subjects will be enrolled in this study.

Subjects who have pre-screened for the relevant HLA alleles and NY-ESO-1 antigen will sign the study Informed Consent Form (ICF) and enter the Screening Phase in this protocol to determine eligibility for the study. The Screening Phase starts from the time the subject signs the ICF until leukapheresis. Eligible subjects then enter the Interventional Phase 1 of the study (first T cell infusion) which runs from the day of leukapheresis until progressive disease (PD).

Subjects will be screened for enrollment into the study according to the eligibility criteria in Section 4.2. Following Screening, subjects meeting all eligibility criteria will undergo leukapheresis to obtain cells for the manufacture of autologous NY-ESO-1^{c259}TCR bearing T cells. Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation. Leukapheresis may also be performed in advance of a subject being eligible for treatment (i.e., before meeting the eligibility criteria prior to lymphodepleting chemotherapy).

When the NY-ESO-1^{c259}T cells are available, subjects will undergo lymphodepleting chemotherapy with cyclophosphamide and fludarabine (Section 5.2), followed by infusion of NY-ESO-1^{c259} transduced T cells in the range of 1 x 10^9 to 8 x 10^9 transduced cells (Section 5.3). Prior to the administration of lymphodepleting chemotherapy, subjects must have failed at least one prior platinum-containing regimen and have PD. All other eligibility criteria will be reconfirmed and baseline tumor measurements obtained. The lymphodepleting chemotherapy may be given as an outpatient procedure but subjects may be hospitalized at the discretion of the Investigator. It is recommended that subjects receive granulocyte-colony stimulating factor (G-CSF) support starting 24 hours after lymphodepleting chemotherapy. It is recommended that the T cell infusion is an inpatient procedure to allow for close monitoring of post-infusion AEs. Subject may be hospitalized for follow-up care post T-cell infusion at the discretion of the Investigator. Section 8 provides guidance for supportive care during T-cell infusion.

The time point for administration of lymphodepleting chemotherapy and subsequent infusion of NY-ESO-1^{c259}TCR bearing T cells will be staggered for the first 3 subjects enrolled. Subjects may receive lymphodepleting chemotherapy as defined in Table 2 only after the previously enrolled subject has had a minimum safety observation period of 21 days following their NY-ESO-1^{c259}T cell infusion. This 21-day observation period shall remain for the first 3 subjects enrolled. If 2 or more subjects among the first 3 subjects enrolled experience a severe study-related toxicity, enrollment will be paused for evaluation by the Sponsor and Investigators, otherwise, an additional 7 subjects will be entered. Refer to Section 4.7 for full details on the stopping rules for this study.

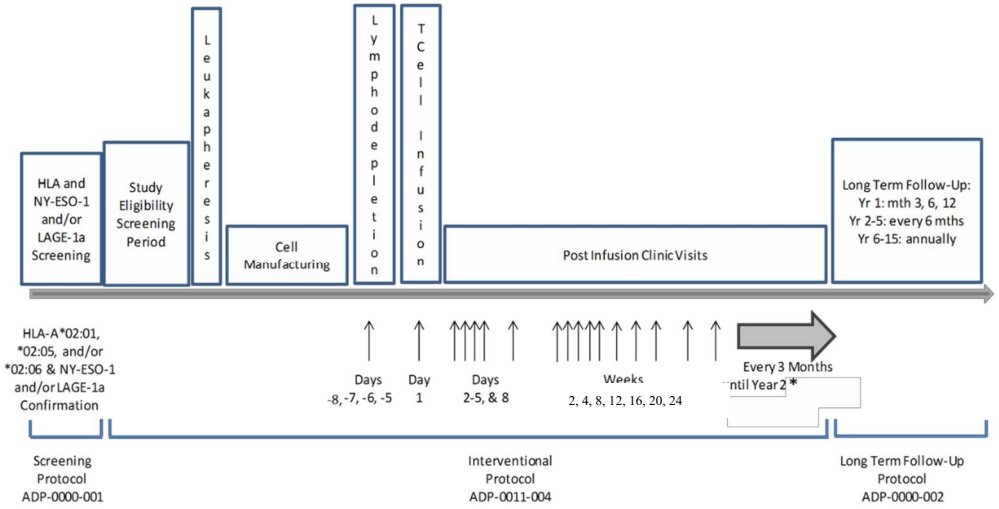
Efficacy, safety, and biomarker assessments to be conducted at each visit are outlined in the Schedule of Procedures (Table 4). Efficacy will be assessed using RECIST v1.1 (Eisenhauer, 2009).

Subjects who have PD following response to the initial infusion but whose tumors continue to express the appropriate antigen target will be eligible for a second infusion with engineered T-cells pending they meet eligibility criteria defined in Section 4.4. Refer to Table 15 for Schedule of Procedures for Second Infusion (Interventional Phase 2).

A subject will be considered to have completed the Interventional Phase of the study when he/she has PD or has died prior to PD, or 2 years after the latest NY-ESO-1^{c259} T cells infusion, whichever is shorter. A subject will be considered completing the Interventional Phase 2 of the study when he/she has PD, or has died prior to PD, or 6 months after the NY-ESO-1^{c259}T cell infusion, whichever is shorter. All subjects completing the Interventional Phase of the study will be rolled over to a long-term follow-up (LTFU) Protocol (GSK208750 [ADP-0000-002]) for observation of delayed AEs for 15 years post-infusion in accordance Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements for gene therapy clinical trials. All subjects will continue to be followed for overall survival during the LTFU phase. If LTFU protocol is not available when a subject completes the Interventional Phase, subject can be followed under this protocol until LTFU protocol becomes available.*

Figure 1 provides a schematic for the study.

Figure 1 Schematic for Study GSK208749 (ADP-0011-004)



*subjects, who have a confirmed response (or have stable disease for >4 months) and subsequently have documented PD and whose tumors continue to express NY-ESO-1 as verified by assay performed in biopsied tissue, can be considered for a second infusion with engineered T cells

3.2 Rationale for Components of Study Design

3.2.1 Screening for HLA and NY-ESO-1

The NY-ESO-1^{c259}T specifically recognizes the HLA-A*02:01, HLA-A*02:05, and HLA- A*02:06-restricted NY-ESO-1 peptide antigen HLA-A*02-SLLMWITQC. NY-ESO-1 and LAGE-1a share the same peptide sequence that is displayed in HLA-A*02:01 on the surface of tumor cells. Therefore, this protocol will select for subjects with these three HLA-A2 allelic variants and whose tumors express

the NY-ESO-1and/or LAGE-1a antigens.

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

3.2.2 T Cell Manufacturing

The Investigational Product (IP) is comprised of autologous CD4 and CD8 T cells that have been transduced with a self-inactivating (SIN) lentiviral vector expressing an affinity enhanced NY-ESO-1 specific TCR. The product of this transduction is polyclonal T cells which are designed to target NY-ESO-1 in tissue. The transfer vector is a SIN lentiviral vector which has been meticulously designed to contain only the minimal genetic elements required for function, and no vector proteins for maximum biosafety (Dull, 1998). Lentiviral vectors are a subset of retroviral vectors thought to have an enhanced safety profile. Many reports provide evidence supporting the relative biosafety of SIN lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the lentivirus Long Terminal Repeat in comparison to the γ retroviral vectors (Maruggi, 2009; Modlich, 2009; Montini, 2009; Montini, 2006).

Cell product typically is ready to be shipped to the site approximately 28 days after leukapheresis. Shipment to clinical sites will ideally be before the start of lymphodepleting chemotherapy; however, exceptions may be made for non-US sites that are unable to store genetically modified cells. In these cases, the cells may be shipped to the site immediately prior to the infusion and stored in the validated cryoshipper.

After the *ex vivo* activation and expansion, the final cellular product is typically >90% T lymphocytes since the culture conditions do not support the growth of macrophages, natural killer or B cells. By the end of the culture period, B cells comprise <2%, natural killer cells <2%, and macrophages <1% of the total culture. Additional details are provided in the NY-ESO-1^{c259}T Investigator Brochure.

3.2.3 Lymphodepletion

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

Recent evidence suggests that preparation for successful engraftment and expansion of gene modified ACT depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia and acute leukemia using ACT including a CAR showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in a previously cyclophosphamide-only preparative regimen (Turtle, 2016).

Based on our experience using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy in a clinical study in synovial sarcoma and the increasing evidence that fludarabine may be a necessary component of the adoptive T cell therapy, the

lymphodepleting regimen in this study consists of fludarabine 30mg/m^2/day at Days -8, -7, -6 and -5 and cyclophosphamide 900mg/m^2/day intravenously at Days -7, -6 and -5 (refer to NY-ESO-1^{c259}T Investigator Brochure). For patients over 60 years of age, see dose modification in Section 5.2. For subjects with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia), the investigator should discuss with the sponsor's medical monitor or designee to determine the need for dose modification of the lymphodepletion regimen.

3.2.4 T Cell Infusion

The investigational product in this study is the infusion of autologous T cells transduced with lentivirus encoding enhanced TCR specific for NY-ESO-1 (refer to Section 5.3 for administration details).

3.2.5 Rationale for NY-ESO-1^{c259} T Cell Dose

Activity seems to be indirectly related to dose administered (depending also on cell expansion and persistence) although high T cell doses may be associated with an increased risk of AE (e.g. cytokine release). Total T-cell doses up to ~100 x 10^9 cells (median of 5 x 10^{10} T transduced T cells with an anti-NY-ESO-1 TCR range of 1.6 x 10^9 to 130 x 10^9) (Robbins, 2011) have been used although the actual products may differ depending on manufacturing methods. Conversely, doses as low as 0.015 x 10^9 (15 million) with CD19 CAR-T cells may also be effective (Porter, 2011).

Current experience with NY-ESO-1^{c259} T (n=100 subjects treated as of January 2019) is with total cell doses in the range of 0.4 x 10^9 – 3.47 x 10^{10} with a transduction level of ~18% – 78% (transduced cell dose range of 0.23 x 10^9 – 14.36 x 10^9). No untoward AEs have been observed in subjects who received higher transduced cell doses (>5 x 10^9 cells). Of the 5 subjects who received <1 x 10^9 transduced cells, 3 subjects had poor expansion and persistence of transduced cells; meaningful clinical responses were not observed in 4 of the 5 subjects. No clear dose response relationship has been observed to-date.

A range of 1 x 10^9 to 8 x 10^9 transduced cells will be administered by a single intravenous infusion on Day 1. If the transduced cell dose is less than the minimum dose of 1 x 10^9, manufacturing of additional transduced T cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range. In the event that no banked leukapheresis product is available, a second leukapheresis may be performed to achieve a dose in the target range.

3.3 Number of Subjects and Duration of Study

The target enrollment for this trial is 10 subjects. In the event, a minimum dose of engineered cells (1 x 10^9 transduced cells) cannot be achieved for a subject, that subject may be replaced with another subject. Up to two subjects may be replaced not to exceed a total of 12 subjects.

Based on the anticipated positive screening rate, study enrollment is expected to continue for approximately 18-24 months. It is estimated that this study will take approximately 24-30 months to complete. The study will be considered complete once the last subject has transitioned to the LTFU protocol.

3.4 Sites

The protocol will be conducted in approximately 15 sites in North America and Europe. The

number of centers is necessary to ensure recruitment in this targeted population. Additional centers may be added at the discretion of the Sponsor.

3.5 Benefit: Risk Assessment

The results of clinical and non-clinical studies conducted with NY-ESO-1^{c259}T are summarized in the Investigator Brochure. This section outlines the potential benefits, risks and the mitigation strategy for this study.

3.5.1 Benefit Assessment

The NY-ESO-1 cancer germline antigen is expressed by RNA sequencing in approximately 12% of lung adenocarcinoma and 26% of squamous cell carcinoma and is highly restricted to the tumor and not expressed in normal healthy adult tissues (NCI, 2016). A subject's T cells can be genetically engineered to recognize tumor antigens. The TCR approach to engineered T cell therapy is attractive because TCRs are capable of recognizing not only cell surface proteins (as is the case with CAR-T cells) but also any internal protein, since TCRs recognize peptide fragments in the context of HLA. In addition, the TCR approach mimics the natural function of the T cell by recruiting the endogenous signaling molecules and adhering to correct spatial orientation between the T cell and its target. These aspects may contribute to enhanced safety and activity of TCR engineered cells.

NY ESO-1^{c259}T is the first Adaptimmune and GSK TCR to be studied in subjects with cancer. As of 27 January 2019, 100 subjects have been treated with NY-ESO-1^{c259}T (engineered using a lentiviral vector) in five clinical trials in the indications of multiple myeloma, synovial sarcoma, myxoid/round cell liposarcoma, melanoma, and ovarian cancer. Objective responses have been observed in the on-going synovial sarcoma study, GSK208466 (formerly ADP-04511) and in the myeloma (transplant) study, 209393 (formerly ADP-01411 [GSK3377794Investigator Brochure 2019;(Rapoport, 2015)]. Additionally, 38 subjects were treated in an Investigator sponsored study conducted by the National Cancer Institute (NCI) (Robbins, 2008; Zhao, 2007), where the T cells were modified using a retroviral vector, expanded using NCI cell processing methods and administered in conjunction with IL-2. HLA-A2 subjects with melanoma and synovial sarcoma tumors expressing NY-ESO-1 were recruited. Eleven of 18 subjects (61%) with synovial sarcoma and 11 of 20 subjects (55%) with melanoma demonstrated objective clinical responses. The estimated overall 3 and 5-year survival rates for subjects with synovial cell sarcoma were 38% and 14% respectively, while the corresponding estimated survival rates for patients with melanoma were both 33% (Robbins, 2015). In addition, two subjects with gastroesophageal cancer have been treated in the ATTACK-OG clinical trial.

Thus, there is good evidence to support the potential therapeutic benefit of NY-ESO-1^{c259}T cells in subjects with advanced or metastatic NSCLC.

3.5.2 Risk Assessment

The known safety profile of NY-ESO-1^{c259}T is based on 100 treated subjects as of 27 January 2019 (see GSK3377794 IB 2019).

In the integrated sponsored trials, 100 subjects have received GSK3377794; fifteen (15) of these subjects [11 subjects in Study 208466 (formerly ADP-04511) and 4 subjects in Study 209393 (formerly ADP-01411)] have received a second infusion of GSK3377794 after progressive disease following response (or prolonged stable disease) to their initial infusion.

Treatment-emergent adverse events (TEAEs) which occurred in ≥50% of subjects following GSK3377794 infusion were nausea (82%), anemia/RBC decreased (79%), neutropenia/neutrophil count decreased (79%), leukopenia/WBC decreased (78%),

thrombocytopenia/platelet count decreased (75%), pyrexia (73%), fatigue (72%), diarrhoea (58%), and lymphopenia/lymphocyte count decreased (50%). There were no apparent significant differences in reported TEAEs between subjects receiving 1 or 2 infusions

Treatment-emergent serious adverse events (SAEs) occurred in 58 (58%) subjects across all studies. Treatment-emergent SAEs occurring in 2 or more subjects following GSK3377794 cell infusion were febrile neutropenia (13%), pyrexia (13%), cytokine release syndrome (CRS) (12%), neutropenia/neutrophil count decreased (10%), dyspnoea (6%), thrombocytopenia/platelet count decreased (5%), dehydration (4%), diarrhoea (4%), hypotension (4%), acute kidney injury (3%), atrial fibrillation (3%), hypoxia (3%), pleural effusion (3%), rash/rash maculo-papular (3%), abdominal pain (2%), anemia/RBC decreased (2%), back pain (2%), bone marrow failure (2%), chills (2%), cough (2%), Guillain-Barré syndrome (2%), leukopenia/WBC decreased (2%), nausea (2%), pneumonitis (2%), Staphylococcal infection (2%), and unspecified graft-versus host disease (GVHD) - other (lung, bone marrow, not specified) (2%). The SAE profile following a second infusion of GSK3377794 was consistent with that experienced for all subjects infused.

Three (3%) subjects experienced treatment emergent fatal SAEs:

- one subject with synovial sarcoma died due to the treatment-related SAE of bone marrow failure on Day 96, despite supportive care for pancytopenia with febrile neutropenia and bacteremia (blood cultures tested positive for Pseudomonas aeruginosa on Day 59 and for cytomegalovirus on Day 69; infections were ongoing at time of death);
- one subject with MRCLS was reported to die due to the treatment-related SAE of cardiac arrest on Day 160. This subject had a Grade 3 cytokine release syndrome (CRS) complicated by supraventricular tachycardia and hypotension related to therapy immediately following infusion. He also had an anterior chest wall mass detected at baseline; contribution of this mass to the cardiac complications is unclear. GSK's assessment of this report indicates that the exact cause of death remains unclear, but not likely related to the study treatment;
- one subject with ovarian cancer died due to disease progression unrelated to treatment, which was reported as an SAE although death due to disease progression is generally excluded from the protocol SAE definition.

There were no fatal SAEs reported among subjects who received a second infusion of GSK3377794.

To help Investigators manage CRS and GVHD, treatment guidance based on published literature was developed and is included in this protocol (refer to Section 8). Study sites are expected to have access to physicians with expertise in bone marrow transplant, and infectious diseases for consultation in the event of a subject developing either CRS or GVHD-like symptomatology. The protocol also includes guidance on the irradiation of transfused blood products to minimize the possibility of transfusion-related GVHD.

GSK are monitoring reports of recurrent pancytopenia after initial bone marrow recovery following pre-conditioning chemotherapy and NY-ESO-1^{c259}T cell infusion. In order to manage this risk, the Sponsor has developed standard protocol guidance on the management of pancytopenia with bone marrow failure following initial bone marrow recovery. Management of bone marrow failure (aplastic anemia) and related cytopenias is challenging, with no clearly established guidelines regarding immunosuppression. Therefore, treatment is

largely supportive, including transfusions and treatment of infections. Guidance includes a recommendation to consult with physicians with expertise in the management of aplastic anemia and infectious diseases.

To manage the risk of CRS, GVHD, and pancytopenia in the NY-ESO-1^{c259}T program, specific AE pages will be implemented in the electronic Case Report Form (eCRF) to carefully document these events to enable evaluation and identification of potential risk factors.

The potential risk of non-infectious encephalopathy, which may be due to the inflammation in the brain following TCR T-cell infusion, is mitigated by the exclusion of participants with brain metastases with features associated with such risk. Grading, monitoring and managing of encephalopathy syndrome (ES) are described in Section 8.9.

The potential risks of replication competent lentivirus (RCL) and insertional oncogenesis (IO) are being monitored in accordance with FDA guidance (refer to Section 10).

Acute inflammatory demyelinating polyneuropathy / Guillain-Barré Syndrome (GBS) developed in two subjects who received the NY-ESO-1^{C259}T cells following infusion. Therefore, subjects with prior or active demyelinating disease will be excluded from the study. Neurologic consultation is required for patients with Grade 2 or higher neurologic events of a ≥7 day duration. Additionally, any potential future recurrence of GBS will lead to a pause in study enrolment and stopping of treatment until further investigation.

Additional experience in clinical trials is required to confirm the incidence of these and other risks. The goal of the risk management measures is to maximize the chance of therapeutic benefit while mitigating and better understanding the risks of treatment with NY-ESO-1^{c259}T cell therapy.

3.5.3 Overall Benefit: Risk Conclusion

Subjects with advanced or metastatic NSCLC who have progressed following other therapies, constitute a population with a high unmet medical need. Data from preclinical studies support the efficacy, specificity and safety of NY-ESO-1^{c259}T cells. Clinical data from subjects summarized in the Investigator Brochure and the NCI study (Robbins, 2015,; GSK3377794 IB 2019), demonstrate the safety and activity of NY-ESO-1^{c259}T cells sufficiently to warrant clinical investigation in subjects with NSCLC.

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

4.1 Overview

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

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

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

4.2 Eligibility Criteria for Study Participation (Prior to Leukapheresis)

4.2.1 Inclusion Criteria

1. Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH GCP Guidelines and applicable local regulations.
2. Subject has agreed to abide by all protocol required procedures including study related assessments, and management by the treating institution for the duration of the study and long-term follow up.
3. Subject is ≥18 years of age on the day of signing informed consent.
4. Subject has a diagnosis of histologically or cytologically confirmed advanced non-small cell lung cancer (Stage IIIB or IV) or recurrent disease.
5. Subjects with known EGFR mutations or ALK or ROS1 gene rearrangements must have failed (PD or unacceptable toxicity) prior EGFR or ALK or ROS1 tyrosine kinase inhibitor, respectively (PD or unacceptable toxicity). There is no limit to lines of prior anti-cancer therapy.
6. Subject has measurable disease according RECIST v1.1 criteria (Eisenhauer, 2009).
7. Subject is HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive.
8. Subject's tumor (either an archival specimen or a fresh biopsy if archival tissue is unavailable) has been pathologically reviewed by an Adaptimmune- / GSK-designated central laboratory confirming NY-ESO-1 and/or LAGE-1a expression.
9. Subject has Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 (Oken, 1982).
10. Subject has and anticipated life expectancy >3 months.
11. Subject has left ventricular ejection fraction ≥50%.
12. Subject is fit for leukapheresis and has adequate venous access for the cell collection.
13. Male or Female. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer.

- Refrain from donating sperm

Plus either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

b. Female Participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

14. Is not a woman of childbearing potential (WOCBP) as defined in Section 6.3 OR
    - Is a WOCBP (as defined in Section 6.3) who will agree to use a barrier method (male condom) and use a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Section 6.3 during the intervention period and for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer. WOCBP should also agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.

      If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

      The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
15. Subject must have adequate organ function as indicated by the following laboratory values in Table 1:

Table 1 Laboratory Values to Define Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥1.0 x 10^9/L (without G-CSF support)
Platelets	≥75 x 10^9/L
Hemoglobin	>80 g/L (without transfusion support within 7 days from start of leukapheresis)
Coagulation	
Prothrombin Time or International Normalized Ratio	≤1.5 x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Partial Thromboplastin Time	≤1.5 x ULN unless receiving therapeutic anticoagulation.
Renal	
Calculated or measured creatinine clearance [1]	≥40 mL/min
Hepatic	
Serum total bilirubin	≤1.5 x ULN (unless subject had documented Gilbert's Syndrome)
Alanine aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase	≤2.5x ULN

1. In subjects <65 years of age creatinine clearance will be calculated using the Cockcroft-Gault Method:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight kg}}{72 \times \text{serum creatinine mg/dL}} (\times\ 0.85 \text{ in females})$$

Subjects ≥65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine ethylenediamineteraacetic acid (EDTA) glomerular filtration rate (GFR) measurement, according to standard practice at the treating Institution.

4.2.2 Exclusion Criteria

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

1. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per Investigator assessment).

   NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice or cirrhosis.

2. Subject has received:

   - Cytotoxic chemotherapy within 2 weeks prior to leukapheresis;

- Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors) or biological therapy with no wash-out times required;
- Corticosteroids or any other immunosuppressive therapy within 2 weeks prior to leukapheresis;
  NOTE: recent or current use of inhaled or topical steroids is not exclusionary.
- Tyrosine kinase inhibitor (e.g. erlotinib, gefitinib) and any other anti-cancer treatment within 1 week prior to leukapheresis;
- Investigational treatment within 4 weeks prior to leukapheresis;
- Experimental anti-cancer vaccine within 2 months prior to leukapheresis in the absence of response or in the opinion of the Investigator is responding to an experimental vaccine given within 6 months prior to leukapheresis;
- Any prior gene therapy using an integrating vector.

3. Subject has toxicity from previous anti-cancer therapy that has not recovered to Grade ≤1 prior to enrolment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with existing pneumonitis as a result of radiation are not excluded; however, subjects cannot be oxygen dependent. Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g. peripheral neuropathy) can be enrolled on a case-by-case basis with prior consultation and agreement with the Sponsor Study Physician.
4. Subject has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to cyclophosphamide, fludarabine, or other agents used in the study.
5. Subject has central nervous system (CNS) metastases except if, on a case by case basis after risk-benefit evaluation in consultation with the Sponsor Medical Monitor or designee (all below points apply):
   - Low CNS disease burden
   - Asymptomatic
   - Clinically stable
   - No history of bleeding within CNS metastases
   - No lesions in the brain stem
   - Not requiring escalating anti-epileptic treatment
   - Not requiring treatment with steroids
   - Not treated with whole brain radiotherapy within the prior 4 weeks
   - Not with leptomeningeal disease or carcinomatous meningitis

   Note: Treatment with focal radiotherapy may be allowed (for example, gamma knife radiosurgery) with at least 2-week wash-out period
6. Subject has active brain metastases or leptomeningeal metastases. Subjects with prior history of brain metastasis who have undergone local therapy (i.e., metastatectomy and/or

radiation) and show no evidence of local recurrence or progression over the past 3 months prior to Screening are eligible.

7. Subject has other active malignancies besides NSCLC within 3 years prior to Screening. **Exceptions:** adequately treated malignancies not likely to require therapy (e.g., completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma). Subjects must be in complete remission from prior malignancy in order to be eligible to enter the study.
8. Subject has unintended weight loss >10% in 6 months preceding study entry.
9. QTc > 450 msec or QTc > 480 msec for patients with Bundle Branch Block (BBB). NOTES:
    - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
    - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.
    - For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
10. Subject has uncontrolled intercurrent illness including, but not limited to:

- Ongoing or active infection;
- Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class >1; uncontrolled clinically significant arrhythmia in last 6 months; acute coronary syndrome (angina or myocardial infarction) in last 6 months;
- Inadequate pulmonary function with mechanical parameters <40% predicted (forced expiratory volume in 1 second [FEV1], forced vital capcity [FVC], transfer factor of the lung for carbon monoxide [TLC], diffusing capacity of the lungs for carbon monoxide [DLCO]);
- Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded; however, subjects cannot be oxygen dependent);
- Prior or active demyelinating disease.

11. Subjects who in the opinion of the Investigator will be unlikely to fully comply with protocol requirements.
12. Subject has active infection with human immonodeficicency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human lymphotropic virus (HTLV) as minimally defined below:

- Positive serology for HIV;
- Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. For potent immunosuppressive agents, subjects with presence of hepatitis B core antibody (HBcAb) should also be excluded.

  –
- Active hepatitis C infection as determined by hepatitis C RNA;
- A subject who is HCV antibody positive will be screened for HCV RNA by any RT polymerase chain reaction (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.

13. Subject is pregnant or breastfeeding.

4.3 Additional Eligibility Criteria (Prior to Lymphodepleting Chemotherapy)

Prior to lymphodepleting chemotherapy, all subjects must meet all the inclusion and exclusion in Section 4.2 and the following inclusion criterion:

1. Subject has disease progression.
2. Subject has failed at least one prior platinum-containing regimen. Subject may have received PD-1 or PDL-1 inhibitors. There is no limit to lines of prior anti-cancer therapy.

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

1. Subject has received:

- Cytotoxic chemotherapy within 3 weeks prior to lymphodepleting chemotherapy;
- Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors) or biological therapy within 4 weeks prior lymphodepleting chemotherapy;
- Corticosteroids or any other immunosuppressive therapy within 2 weeks prior to lymphodepleting chemotherapy;
  NOTE: A brief course of oral corticosteroids limited to less than 7 days is not exclusionary if completed 2 weeks prior to lymphodepleting chemotherapy; a recent or current use of inhaled or topical steroids is not exclusionary.
- Tyrosine kinase inhibitor (e.g. erlotinib, gefitinib) and any other anti-cancer treatment within 1 week prior to lymphodepleting chemotherapy.
- Major surgery within 4 weeks prior to lymphodepleting chemotherapy; subjects must have recovered from any surgical-related toxicities in the opinion of the Investigator;
- Radiotherapy that involves the lung or mediastinum within 3 months prior to lymphodepleting chemotherapy; however, electron beam radiotherapy to superficial structures in the chest is permitted.
  NOTE: there is no washout period for palliative radiation to non-target organs other than the lung and mediastinum. If radiation was to an intended target lesion within 3 months of baseline imaging studies, and the lesion is progressing within this time frame it may be

considered as a target lesion after review and discussion with the Sponsor.

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

Prior to receipt of a second T-cell infusion, all subjects must remain eligible to receive manufactured T-cell product as defined in Section 4.2 and Section 4.3 and meet the following inclusion criteria:

1. Subject has had a documented confirmed response [partial response (PR) or complete response (CR)] or stable disease >4 months followed by confirmed PD after the first T-cell infusion.
2. A second T-cell infusion is recommended by the Investigator.
3. Subject has a new tumor biopsy confirming NY-ESO-1 and/or LAGE-1a expression.
4. Subject has voluntarily agreed to receive a second T-cell infusion by giving written informed consent.
5. Subject has toxicity from first T-cell infusion that resolved to Grade ≤1.
6. Manufactured T-cell product must be available.

- In cases where previously manufactured T-cell product is not available, any residual leukapheresis product from collections prior to receipt of the gene modified T cells will be utilized for a new product manufacture.
- In cases where residual leukapheresed product is not available, subjects can agree to be re-leukapheresed for cells only in circumstances where there are no detectable gene modified cells.

Furthermore and prior to receipt of a second T-cell infusion, a subject meeting the following criterion is not eligible for a second T-cell infusion:

1. Subject with any Grade 4 CRS or clinically life-threatening (Grade 4) AEs deemed at least possibly related to the NY-ESO-1^{c259}T cell product by the Investigator and study Sponsor reported during the first T-cell infusion.
   NOTE: any subject meeting this exclusion criterion might be eligible to receive a second T-cell infusion after evaluation of all available subject data by the Sponsor and Institutional Review Board/Independent Ethics Committee (IRB/IEC) and their subsequent approval.

4.5 Completion of the Interventional Phases

A subject will be considered completing the Interventional Phase 1 of the study when he/she has PD or has died prior to PD, or 2 years after the NY-ESO-1^{c259}T cell infusion, whichever is shorter. A subject will be considered completing the Interventional Phase 2 of the study when he/she has PD, or has died prior to PD, or 6 months after the NY-ESO-1^{c259}T cell infusion, whichever is shorter. All subjects completing the Interventional Phase of the study will enter the LTFU study for observation of delayed AEs during the 15 years post-infusion in accordance with FDA and EMA regulations (FDA, 2006a; EMEA, 2009). If LTFU protocol is not available when a subject completes the Interventional Phase, subject can be followed under this protocol until LTFU protocol becomes available. This study (GSK208749 [ADP-0011-004]) will be considered complete when the last subject has rolled over into the LTFU protocol.

4.6 Subject Withdrawal

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or Institution. However, the Investigator must make every reasonable effort to keep each subject on study for the whole duration of the trial. 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., where possible, 3 telephone calls and, if necessary, 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'.

If a participating subject withdraws consent, all final end of study assessments should be performed, if possible on the day the decision is made to take the subject off-study or as soon as possible thereafter. All the results of the evaluations and observations, together with a description of the reasons for study withdrawal, must be recorded in the medical records and eCRF. The following are some of the justifiable reasons for the Investigator to withdraw a subject from study:

- Withdrawal of consent.
- Did not receive any NY-ESO-1^{c259} T cell (Refer to Section 9.1 and Section 9.2 for continued monitoring of AEs/SAEs following study procedures).

If a subject who has consented to participate in pharmacogenetics research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options concerning the pharmacogenetics sample, if already collected:

- Pharmacogenetics research continues as per the subject's consent; or,
- Any remaining sample is destroyed

If a subject withdraws consent from the pharmacogenetics research or requests sample destruction, the Investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep study information collected/generated up and until that point.

If the subject voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanently discontinuation on the eCRF.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Schedule of Assessments Table (see Section 7).

4.7 Consideration for Temporary Suspension of Enrollment

Throughout the conduct of the study, all safety data will be closely monitored for each subject on an ongoing basis. Based on the severity of the AEs, the degree of T cell expansion, indicators of potential anti-tumor activity, and other factors, a recommendation

whether to suspend treatment, or continue enrollment will be made with input from the Safety Review Team (SRT), Sponsor and Investigators. Final decisions to halt or modify the study will be made by the Sponsor.

Study will pause enrolment and stop treatment for all participants if any of the following

events occur pending submission to Regulatory Agencies and review by IRBs/ECs, and the Sponsor:

- Any event of Guillain-Barre syndrome (GBS) as diagnosed by a neurologist according to diagnostic guidance for GBS [Fokke, 2014] (refer to Section 10.4).
- A case of documented symptomatic progressive cerebral edema confirmed by an expert neurological examination and CT/MRI, that is not responding to treatment.
- Any death occurs that is deemed to be at least possibly related to the NY-ESO-1^{c259}T cell product by the Investigator and the Sponsor; or
- Two or more Grade 4 autoimmune events deemed probably or definitely related to the NY-ESO-1^{c259}T cell product by the Investigator and the Sponsor; or
- A biologically functional positive Replication Competent Lentivirus (RCL) after 2 confirmed positive tests by PCR

Following assessment by the Sponsor, enrollment and dosing may resume if agreed upon by the Sponsor, and Regulatory Authorities.

4.8 Liver Safety: Required Actions and Follow-up Assessments

Level 1 Monitoring

In the event that the subject develops elevations in liver function test (LFT) parameters as defined below, an increase to liver chemistry monitoring i.e. at weekly intervals, will apply.

Liver Chemistry Monitoring Criteria Level 1	
Criteria	**Actions**
ALT ≥3x ULN **but** ALT <5x ULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant must return weekly for repeat liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If, during monitoring, ALT increases to ≥ 5xULN , or remains ≥3x ULN for ≥4 weeks, or if total bilirubin increases to ≥2xULN, refer to Level 2 monitoring guidance below. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

Level 2 Monitoring

In the event that the subject develops elevations in LFT parameters as defined below, an increase to liver chemistry monitoring at more frequent intervals i.e. twice weekly, will apply.

Liver Chemistry Monitoring Criteria Level 2	
ALT absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
International normalized ratio (INR)[2]	ALT ≥ 3xULN **and** INR>1.5
Symptomatic[3]	ALT ≥ 3xULN and associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow-Up Assessments**
• Report the event to GSK **within 24 hours** • Complete the CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (pre-Gene Therapy) (see **MONITORING** below) **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow-up assessments within **24 hrs** • Monitor participants twice-weekly until liver chemistries resolve, stabilize or return to within baseline (pre-Gene Therapy) • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow-up assessments within **24-72 hrs** • Monitor participants at least weekly until liver chemistries resolve, stabilize or return to within baseline (pre-Gene Therapy)	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Serum creatine phosphokinase and lactate dehydrogenase • Fractionate bilirubin, if total bilirubin≥2xULN • If possible, obtain peripheral blood for persistence of genetically modified cells • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • 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 computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms

1. Serum bilirubin fractionation should be performed if testing is available. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants.
3. 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 believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.

5 STUDY TREATMENTS

5.1 Leukapheresis

Subjects who complete screening procedures and who meet all eligibility criteria defined in Section 4.2 will be eligible to undergo leukapheresis to obtain starting material for the manufacture of autologous NY-ESO-1^{c259}T. Prior to leukapheresis, an absolute lymphocyte count of ≥0.5 x 10^9/L and the CD3 count ≥200/μL is recommended.

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

Once NY-ESO-1^{c259}T cell product has been manufactured and received at the site, eligible subjects will proceed to have lymphodepleting chemotherapy and infusion of IP as detailed in Section 5.2 and Section 5.3, respectively.

5.2 Lymphodepleting Chemotherapy

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

When the NY-ESO-1^{c259}T cells have completed manufacture, have fulfilled release criteria, and are available for infusion at the site, fludarabine and cyclophosphamide will be administered as lymphodepleting chemotherapy as described in Table 2 to all subjects. For subjects with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia), the investigator should discuss with the sponsor's medical monitor or designee to determine the need for dose modification of the lymphodepletion regimen.

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

Table 2: Lymphodepleting Chemotherapy Treatment Regimen for GSK208749 (ADP-0011-004)

Lymphodepleting chemotherapy					**Recommended prophylaxis and supportive medication**
Day	**Drug**	**Dose**	**Route**	**Administration[1]**	**Infection:** on admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Section 8.2 or in line with institutional standard practice. **Hydration:** ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions **Mesna:** may be given to prevent urotoxicity per institutional guidelines or as recommended in Section 5.2.2. **G-CSF:** recommend starting 24 hours after the last cyclophosphamide infusion until resolution of neutropenia in accordance with ASCO guidelines (Smith , 2015) or institutional practice (refer to Section 8.8.1)[5].
-8	**Fludarabine[2, 3]**	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins[4]	
-7	**Fludarabine[2, 3]**	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins[4]	
	Cyclophosphamide[3]	900 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-6	**Fludarabine[2, 3]**	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins[4]	
	Cyclophosphamide[3]	900 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-5	**Fludarabine[2, 3]**	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins[4]	
	Cyclophosphamide[3]	900 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-4	start **G-CSF[6]**				
-3					
-2					
-1					
1	**NY-ESO-1^{c259}T cell infusion[5]**				

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

1 Or per institutional guidelines
2 Fludarabine dose will be adjusted in renal impairment as described in Section 5.2.1.
3 For subjects ≥ 60 years of age or for participants with documented history of severe and prolonged cytopenia, see Section 5.2.1..
4 Concentration ≤1mg/mL
5 Administration of NY-ESO-1^{c259}T infusion is described in Section 5.3
6 Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose 24 hours after the last chemotherapy administered

5.2.1 Lymphodepletion Dose Modification

For participants ≥ 60 years old, the recommended lymphodepleting regimen will be as follows:

- Fludarabine at 30mg/m^2 for 3 days (Day -7 to Day -5)
- Cyclophosphamide at 600mg/m^2 (Day -7 to Day -5)

In case of participants with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia), the investigator should discuss with the sponsor's medical monitor or designee the opportunity for potential lymphodepletion dose adjustment.

5.2.2 Fludarabine dose adjustment for renal impairment

Dose of fludarabine will be adjusted for subjects with renal dysfunction as described in Table 3:

Table 3: Fludarabine Dose Adjustment

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

5.2.3 Mesna

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

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

5.3 T Cell Infusion

The autologous T cells transduced with lentivirus encoding enhanced TCR specific for cancer-testis antigen NY-ESO-1 is the investigational product in this study.

Subjects will receive a single dose of NY-ESO-1^{c259}T five days after completing the lymphodepleting chemotherapy. This is considered Day 1 and all procedures and assessments to be performed are listed in the Schedule of Procedures (Table 4).

5.3.1 Premedication

Thirty to sixty (30-60) minutes prior to cell infusion, subjects will be premedicated against potential infusion reactions with antihistamines and acetaminophen (paracetamol) according to institutional practice. Steroids should not be administered as premedication for T cell infusion because they are lymphotoxic and inhibitory to the T-cell product.

5.3.2 T Cell Infusion

On Day 1, the subject will receive thawed NY-ESO-1^{c259}T by intravenous infusion. Prior to infusion, two clinical personnel in the presence of the subject, will independently verify and confirm that the information on the infusion bag is correctly matched to the subject, as per the participating center's blood bank procedures.

NY-ESO-1^{c259}T must not be thawed until immediately prior to infusion. The cells can be

thawed either in a water bath at the subject's bedside or in a centralized facility, according to institutional standard procedures. The cells must be infused without delay, and if thawed centrally, must be transported to the subject by appropriately trained clinical staff, to preserve the chain of custody. The cell product must not be washed or otherwise processed. It is expected that the infusion will commence within approximately 10 minutes of thawing and complete within 45 minutes of thawing to minimize exposure of the cell product to cryoprotectant. If the cells are provided in multiple bags, the second bag must not be thawed until half the first has been infused without reaction.

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

NY-ESO-1^{c259}T will be administered using a dual spike infusion set by gravity over 15-30 minutes in the absence of reaction. It is recommended that the cells are infused without a filter, however if a filter is required by institutional practice the pore size must not be smaller than 170 µm. Infusion pumps must not be used. For administration of the cells, 100 - 250 ml of 0.9% sodium chloride should be connected to the second lumen of the infusion set, used to prime the line, and then the lumen closed. On completion of the infusion of a bag of NY-ESO-1^{c259}T, the main line should be closed and approximately 50 ml saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided. On completion of the cell infusion the set should be flushed using additional saline from the attached bag.

In the event of adverse reaction to the cell infusion the infusion rate should be reduced and the reaction managed according to institutional standard procedures (refer to Section 8.1). Steroid treatment should be avoided unless medically required. In the event a subject develops 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.

The day of T cell infusion may be delayed in subjects with significant complications of chemotherapy if according to the Investigator it is in the best interest of the subject. The timing of all assessments post-infusion will be calculated with reference to the T-cell infusion date. Subjects who have undergone leukapheresis but do not receive the T-cell infusion will be replaced. Cytopenias alone should not be a reason to delay T-cell infusion unless complications are present.

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

5.4 Second T Cell Infusions (Interventional Phase 2)

Following the initial infusion, subjects, who have a confirmed response (or have stable disease for >4 months) and subsequently have documented PD and whose tumors continue to express NY-ESO-1 and/or LAGE-1a as verified by assay performed in biopsied tissue, can be considered for a second infusion with engineered T cells. Subjects must continue to meet all eligibility criteria for the study in addition to those specified in Section 4.4 prior to receiving a second infusion.

The second infusion may be given within 6 months of PD and after at least 12 weeks have elapsed from the time of previous infusion. During the period in which the subject is being considered for a second infusion, new or changes in AEs as defined in Section 9 must be recorded in the electronic data capture (EDC) system and blood for persistence (for safety)

and RCL monitoring must be collected at the time points noted in the Schedule of Procedures Table 4. However, no other clinical assessments or procedures are required until the subject is consented for the Interventional Phase 2.

Some subjects may need to have another leukapheresis. Prior to screening subjects for the Interventional Phase 2 (second T cell infusion), it should be determined if the subject has either 1) previously manufactured T cell product available or 2) any residual leukapheresis product that can be utilized for a new T cell product manufacture. In cases where T cell product or leukapheresed product is not available, the subject can agree to undergo another leukapheresis for cells only in circumstances where there are no detectable gene modified cells. Table 15 provides the Schedule of Procedures for those subjects who will not require another leukapheresis collection of cells. For subjects who do require another leukapheresis, please follow the clinical procedures and assessments noted in the Screening phase, Leukapheresis, and Baseline visits as outlined in Table 4 with the exception of the following procedures, which are not required:

- Demographics
- Tobacco use
- Blood sample for Pharmacogenetic analysis
- Tumor biopsy at Baseline

  NOTE: If a fresh biopsy was taken to confirm continued expression of NY-ESO-1 and/or LAGE-1a at time of PD after the first T cell infusion and there is sufficient tumor sample left remaining, this sample may be used as the baseline sample for the Interventional Phase 2. This sample may also be used to assess tumor histology. Otherwise, the baseline biopsy may be collected anytime between two weeks prior to the start of lymphodepleting chemotherapy, with preference closer to the time of infusion.

These subjects will then continue to follow the clinical assessment and procedures outlined in Table 15 from the Lymphodepleting Chemotherapy visit onward.

Subjects that qualify for a second infusion will receive the same lymphodepleting chemotherapy regimen and T cell infusion as received during the first T cell infusion.

6 CONCOMITANT MEDICATION AND TREATMENT

6.1 Prohibited Concomitant Medication and Treatment

The following treatments are prohibited during the Interventional Phase of the study: non-protocol chemotherapy, immune therapy, biological therapy (including targeted therapies with tyrosine kinase inhibitors or monoclonal antibodies), or investigational anti-cancer therapy. Subjects should also not undergo other anticancer locoregional therapies, such as surgical resection or non-palliative radiation. Subjects should not require these therapies before confirmation of PD, and if used, will be considered as having met the PD criterion for efficacy and will rolled over to the LTFU Protocol and will not be eligible for a second T cell infusion.

Refer to Section 4.2.2 and Section 4.3 for details of washout and excluded treatments prior to leukapheresis and lymphodepleting chemotherapy, respectively.

The use of systemic steroids may abrogate the effects of the T cell therapy and therefore; use

is discouraged unless required to manage CRS (refer to Section 8.5 for CRS management) or other significant immune-mediated AEs. According to local standard of care or American Society of Clinical Oncology (ASCO) guidelines (Basch, 2010), steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the IP. Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

6.2 Permitted Concomitant Medication and Treatment

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

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

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

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

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

6.3 Contraception

NY-ESO-1^{c259}T may have adverse effects on a fetus *in utero*. Furthermore, it is not known if NY-ESO-1^{c259}T has transient adverse effects on the composition of sperm.

Definitions:

Woman of Childbearing Potential (WOCBP)

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 WOCBP

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 (as per laboratory parameters for postmenopausal range) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT) when postmenopausal status is in doubt. 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.

Contraception:

Male Participants:

Male participants must agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer.

- Refrain from donating sperm

Plus either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

Female participants:

WOCBP must agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer.

For contraception, subjects who are WOCBP must use a barrier method (male condom) and should comply with one of the following:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods [b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] oral injectable
Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. • Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. • Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

7 SCHEDULE OF ASSESSMENTS AND PROCEDURES

The Schedule of Procedures is provided in Table 4 for Screening and the Interventional Phase 1 of the study. On completion of the Interventional Phase, subjects transition to the LTFU Protocol.

Subjects will have been assigned a unique subject identification number upon signing the ICF for the Screening Protocol, ADP-0000-001. The number assigned will serve as the same subject ID upon qualification and enrollment into the Interventional Phase 1 of this study.

NOTE: A subject will have the same Subject ID in the Screening Protocol (ADP-0000-001), in this study (GSK208749 [ADP-0011-004]), and in the LTFU Protocol (GSK208750 [ADP-0000-002]). Refer to the SPM for further details on assignment of Subject ID.

Study procedures performed as part of standard of care (laboratory assessments, radiologic imaging, including cardiac assessment) prior to signing informed consent can be used for screening if they were performed within the time period prior to leukapheresis as noted in Table 4.

7.1 HLA and Antigen Screening

Subjects identified by the Investigator as possible candidates for the trial must have completed screening under Screening Protocol, ADP-0000-001, to confirm that the subject is HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and with NY-ESO-1 positive tumor prior to conducting the screening procedures in this study.

7.2 Schedule of Procedures

Table 4 Schedule of Procedures (Interventional Phase 1)

	Screening Phase[1]	Interventional Phase 1																												
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																					
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -9**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	**Completion/ Withdrawal[5]**
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**					**±7 days**						**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25-30	31+	
Clinical Assessments and Procedures[6] (refer to Section 7.4 for details)																											
Informed Consent[7]	X_{EDC}																										
Demographics	X_{EDC}																										
Inclusion/ Exclusion	X_{EDC}[8]		X[9]																								
Medical History[10], and Tobacco Use	X		X																								
Physical Exam	X		X					X					X	X										X	X	X	
Prior/Concomitant Medications[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X		X					X					X	X	X	X		X	X		X	X		X	X	X	X
Vital Signs / Height/ Weight[12]	X		X					X[13]	X	X	X	X	X	X													X
ECG	X		X					X			X		X														

	Screening Phase[1]	Interventional Phase 1																												Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																					
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -9**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**					**±7 days**						**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25-30	31+	
ECHO/MUGA	X_{EDC}[4]																										
CT / MRI[14]	X[4]		X																X			X		X	X	X	X
Brain MRI [28]	X		X	See footnote 28																							
ICE[29]				See footnote 29																							
Chest X-ray			X																								
PFTs[15]	X_{EDC}																										
Lymphocyte Subset (CD3/CD4/CD8)	X_{EDC}																										
Hematology	X_{EDC}[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X		X	X	X	X
Coagulation Tests	X[4]		X																								
Pregnancy Test[16]	X		X					X								X			X		X	X	X	X	X	X	X
Urinalysis	X[4]		X																								
Infectious disease markers[17]	X_{EDC}																										

	Screening Phase[1]	Interventional Phase 1																											Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																				
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -9**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**					**±7 days**						**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25-30	31+	
CMV IgG and PCR[18]			X					X						X		X		X	X								
TSH with free T4[19]			X																								
CRP[20]			X					X			X		X	X		X											
Uric acid			X					X											`								
GFR or 24h urine[21]	X		X																								
Adverse Events[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vector Copies (Persistence for Safety)[23]								X													X			X	X[23]	X[23]	
VSV-G DNA (RCL)[24]								X													X			X	X[24]	X[24]	
Leukapheresis, Lymphodepleting Chemotherapy & Investigational Product Administration																											
Leukapheresis		X																									
Fludarabine				X	X	X	X																				

	Screening Phase[1]	Interventional Phase 1																										Completion/ Withdrawal[5]
		Leukapheresis	Baseline	Lymphodepleting Chemotherapy[2]				T-cell infusion[3]	Post-T-cell Infusion																			
Day (D) / Week (W)	**- 28 D[4] of Leukapheresis**		**D -14 to -9**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**					**±7 days**						**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25-30	31+	
Cyclophosphamide					X	X	X																				
NY-ESO-1c259T								X																			
Correlative Studies and Research Assessments (refer to Section 7.5 for details)																											
Pharmacogenetic analysis			X[25]																								
Tumor biopsy[26]			X[26a]																X								X
Liquid biopsy[26b]			X																X								X
Cell phenotype and Functional Assays,			X					X			X		X	X		X			X		X						X
Cytokine Analyses[20] & Humoral Anti-Infused Cell Responses			X					X[27]	X	X	X	X	X	X	X	X			X[27]		X						X

	Screen-ing Phase[1]	Interventional Phase 1																												Completion/ Withdrawal[5]
		Leuka-pheresis	Base-line	Lymphodepleting Chemotherapy[2]				T-cell in-fusion[3]	Post-T-cell Infusion																					
Day (D) / Week (W)	**- 28 D[4] of Leuka-pheresis**		**D -14 to -9**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 8**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W8**	**W 10**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**					**±7 days**						**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25-30	31+	
Vector Copies (Persistence) for Research			X					X	X		X		X	X		X			X		X						X

Abbreviations:ICE = Immune Effector Cell-Associated Encephalopathy; CMV = cytomegalovirus; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computerized tomography; ECG = electrocardiogra ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; FPCP = female patient of childbearing potential; GFR = glomerular filtration rate; MRI = magne resonance imaging; MUGA = multigated acquisition; n/a=not applicable; PCR = polymerase chain reaction; PFT = pulmonary function test; RCL = replication competent lentivirus; TSH = thyroid-stimulati hormone; VSV-G =vesicular stomatitis virus G protein

1. Subjects must have completed screening under Screening Protocol, ADP-0000-001, and confirmed as HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 and/or LAGE-positive tumor prior to conducting the procedures in this visit. All clinical assessments and procedures in this visit must be performed as indicated and recorded in source documents; however, only thos assessments/procedures indicated with bold $\mathbf{X_{EDC}}$ will be recorded in the EDC at this visit.
2. Refer to Section 5.2 for details on prophylaxis therapies, pre-medications, fludarabine dose adjustments according to renal function, and supportive treatments.
3. All samples will be collected and assessments performed prior to T-cell infusion, unless otherwise specified.
4. All clinical assessments required at the Screening visit must be performed within 28 days of leukapheresis, with the exception of lymphocyte subset (CD3/CD4/CD8), hematology, chemistry, coagulatio and urinalysis which must be done within 7 days of leukapheresis. ECHO/MUGA, MRI/CT scan and laboratory assessments performed as standard of care prior to study consent will be acceptable as long as assessment is done within required time period before leukapheresis.
5. If a subject withdraws consent or completes the Interventional Phase 1, all procedures and assessments listed at this visit must be performed, unless done within the previous 30 days.
6. All clinical assessments and procedures must be performed as indicated; however, any clinical assessment or procedure can be performed if clinically indicated at any time
7. Written subject informed consent must be obtained prior to performing any assessment or procedures, unless otherwise specified.
8. Subjects must meet all eligibility prior to leukapheresis as specified in Section 4.2.
9. Subjects must continue to meet all eligibility criteria (Section 4.2) in addition to meeting those prior to lymphodepleting chemotherapy specified in Section 4.3.
10. Medical history will be recorded in the EDC at Screening and Baseline visits; however, any changes in medical history must be recorded in source documents throughout the conduct of the study.
11. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.

[12] Includes temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. Height will be collected at the Screening visit only.
[13] Vital signs on day of T cell infusion should be taken pre-infusion, and at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started
[14] If a subject is found to have a tumor response or PD by imaging, a follow-up confirmation scan must be done no earlier than 4 weeks following the scan when response or PD first seen. A subject is not considered to have a response or PD until follow-up scan confirms the finding.
[15] Includes FEV1, FVC, TLC, and DLCO parameters to determine eligibility as described in Exclusion criterion #10 .
[16] FPCP must have a negative urine or serum pregnancy test.
[17] Includes HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochaete bacterium). Refer to Exclusion criterion #12 for details on required testing for eligibility. Testing for infectious disease markers is required only at Screening and does not need to be repeated at Baseline to satisfy eligibility criteria.
[18] Only subjects who are CMV IgG seropositive at Baseline will continue to be monitored for CMV viremia by CMV DNA PCR post Baseline.
[19] A free T4 test should be performed in subjects who have an abnormal TSH function test (high or low).
[20] If CRS is suspected, cytokine and C-reactive protein levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.
[21] Only to be done in subjects ≥65 years of age to measure renal function.
[22] Adverse events should be reported as noted in Section 9.
[23] Persistence of gene modified cells in subjects will be monitored at Months 3, 6, and 12 post-infusion, then every 6 months until 5 years post-infusion and annually from year 6-15 post infusion. If no gen modified cells are detected for 3 consecutive assessments post-infusion, and subject is ≥5 years post-infusion, then sample collection maystop.
[24] If RCL tests are negative at all time points during the first year, then samples will be collected annually and archived for up to 15 years post infusion or until assessments for persistence have ended However, if VSV-G DNA copies are detected at any time point in the first year post-infusion, refer to the safety monitoring procedures in Section 10.5.
[25] If pharmacogenetic sample collection is not done at Baseline, it may be done at any other subsequent visit in the Interventional Phase 1. Collection of a pharmacogenetic sample is optional and all subjects must provide consent for sample collection and analysis.
[26] Core needle biopsies for research are at Baseline, week 8, and at confirmation of PD, with the exception of subjects for whom there is no safely accessible tumor tissue. 26a.) If a fresh biopsy was taken for NY-ESO-1and/or LAGE-1a confirmation screening in Screening Protocol, ADP-0000-001, and there is sufficient tumor sample left remaining, this sample may be used as the baseline sample. Otherwise, the Baseline biopsy may be collected anytime two weeks prior to the start of lymphodepleting chemotherapy, with preference closer to the time of infusion. 26b.) Blood sample from which cell-free DNA (cfDNA), cell-free RNA (cfRNA), circulating tumor cells (CTC), and exosomes may be extracted should match tumor biopsy time points.
[27] Pre-infusion and Week 8 blood collection is for both Cytokine and Humoral anti-infused cell responses, and is collected in one 3 ml tube.
[28] Brain MRI (or CT Scan if MRI not feasible) should be obtained in all subjects at the time of screening. Baseline brain MRI should be repeated if more than 4 months have elapsed prior to lymphodepletion.
[29] Immune Effector Cell-Associated Encephalopathy (ICE) should be measured on the day of NY-ESO-1c259T cell infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. Subjects with know brain metastases should be monitored at least twice per day for the first 5 days following NY-ESO-1c259T cell infusion. If a subject is found to have Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), the ICE neurological assessment tool , should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

Table 5 Schedule of Procedures – Long Term Follow-up

Time post-infusion												
	Year 1			Year 2		Year 3		Year 4		Year 5		Years 6-15
Months	3	6	12	18	24	30	36	42	48	54	60	Annually
Visit window	± 2 weeks		± 3 month									± 6 months
Safety Assessments												
Medical History and Physical Exam[1]		X	X	X	X	X	X	X	X	X	X	X
Mutagenic agents, other investigational agents or anti-cancer therapies		X	X	X	X	X	X	X	X	X	X	X
Delayed Adverse Events and Serious Adverse Events[2]		X	X	X	X	X	X	X	X	X	X	X
Pregnancy test for WOCBP[3]	<==========X[3]==========											
Hematology		X	X		X		X		X		X	X[4]
Serum chemistry		X	X		X		X		X		X	X[4]
Allogeneic SCT	X	X	X	X	X							
Laboratory Assessments												
VSV-G DNA (RCL) for safety	X	X	X		X		X		X		X	X[4]
Transgene Copies (Persistence) for safety	X	X	X	X	X	X	X	X	X	X	X	X
Other Assessments												
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: RCL=replication competent lentivirus; SCT=stem cell transplant; VSV-G =vesicular stomatitis virus G protein

1. New medical history/medications/chemotherapies.
2. Delayed Adverse Event and Serious 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 immune-related hematologic disorder
   - Serious infections (including opportunistic)
   - Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy

3. For women of child bearing potential (WOCBP), pregnancy testing should be conducted during contraception period only as defined in Section 5.1. When pregnancy testing is performed at visits where hematology sample is collected, blood pregnancy testing will be done. At visits where hematology sample is not collected, urine pregnancy test is acceptable unless serum testing is required by local regulation or IRB/IEC.
4. In year 6-15, these assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 10.3) then laboratory assessments are discontinued.

7.3 Screen Failures

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

7.4 Clinical Assessments and Procedures

7.4.1 Medical history

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

7.4.2 Physical Examination and Measurement of Vital Signs

At Screening, subjects will undergo a physical examination including weight, height and measurement of their vital signs (temperature, pulse, respirations, oxygen saturation, and blood pressure). The frequency of physical examination, weight and vital signs assessments at subsequent visits is specified in the Schedule of Procedures (Table 4).

7.4.3 Performance Status

At Screening, performance status will be measured using the ECOG performance scale (refer to Appendix 2). It is recommended, where possible, that a subject's ECOG be assessed by the same person throughout the study. The frequency of the ECOG assessment is specified in the Schedule of Procedures (Table 4).

7.4.4 Clinical Safety Assessments

Subjects will be assessed for AEs throughout the study. AEs are to be graded by NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. All AEs must be recorded in the eCRF. Additionally, subjects will be monitored for RCL and persistence throughout the study as described in Section 10.1 and Section 10.3, respectively.

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

7.4.5 Laboratory Assessments

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

Women subjects of childbearing potential must have a negative pregnancy test at Screening and prior to starting lymphodepleting chemotherapy.

Refer to Schedule of Procedures (Table 4) for information regarding the frequency of these assessments and Appendix 3 for details on these local laboratory tests.

7.4.6 Cardiac and Other Assessments

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

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

- ECGs (refer to Appendix 3 for the ECG parameters required)
- A chest x-ray will be performed at Baseline. Additional x-rays should be performed if clinically indicated.
- Brain MRI will be performed at baseline for all participants and as clinically indicated thereafter (see Section 8.9.2).
- ICE assessment as described in Section 8.9.2 at the timepoints indicated in the Schedule of Procedures.
- Pulmonary function tests will be performed at Screening to determine eligibility (refer to Section 4.2.2 for the parameters required)

Please refer to Schedule of Procedures (Table 4) for information regarding the frequency of these assessments.

7.4.7 Tumor Response Assessments

Tumor assessments for response and PD will be evaluated at Baseline (within 1 week of lymphodepleting chemotherapy), Week 8, Week 16, Week 24, every 3 months until Year 2 and then every 6 months thereafter until PD, according to RECIST v1.1 (refer to Appendix 4) (Eisenhauer, 2009).

Imaging scans of the chest, abdomen and pelvis should be performed at Baseline and all subsequent visits. Acceptable imaging modalities for this study include:

- Diagnostic-quality computerized tomography (CT) scan with oral and/or IV iodinated contrast of the chest and abdomen/pelvis (CT is the preferred modality for tumor assessments);
- Magnetic resonance imaging (MRI) of the abdomen/pelvis acquired before and after gadolinium contrast agent administration and a non-contrast enhanced CT of the chest, if a subject is contraindicated for contrast enhanced CT;
- MRI of the extremities per site standard of care, if clinically indicated;
- Digital photographs of skin lesions including a ruler for estimating the size of the lesion.

Throughout the study, the same imaging modality and image-acquisition protocol (including the use of IV contrast) should be used consistently across all time points for individual subjects to allow uniform comparison of lesions.

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

To allow time for the immune response to become apparent and for potential transient inflammatory reaction of the disease to the treatment ('tumor flare'), response will not be assessed before 4 weeks post infusion of NY-ESO-1^{c259}T unless there is unequivocal clinical evidence of deterioration. Responses or progression should be confirmed by repeat imaging scan performed not earlier than 4 weeks after the criteria for response or progression was first met. Determinations of PD will be based upon RECIST v1.1.

For subjects who have new lesions, response by irRECIST (Nishino, 2013) will be assessed by the Investigator for exploratory purposes but will not be used to formally assess disease response or progression. For new lesions, information on whether the lesion is measurable or non-measurable will be recorded in the eCRF. The measurements of measurable lesions will also be recorded.

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

7.4.8 Long-Term Follow-up

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

Due to the nature of the treatment, participants are required to be followed for up to 15 years after treatment with genetically modified T cells according to FDA and EMA guidance [FDA, 2006b, FDA, 2010]. Delayed AEs are defined as those events that fall into one or more of the 6 categories listed below and which occur either more than one year following GSK3377794 infusion or after disease progression, whichever occurs first. In the event a subject has not progressed 1 year following GSK3377794 infusion, delayed AEs will be collected in Interventional Phase of study. Delayed AEs which occur post progression will be collected as part of the LTFU phase of the current study or in the LTFU Study (208750), contingent upon formal transfer of subject to Study 208750.

- New malignancies
- New incidence or exacerbation of a preexisting neurological disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of an immune-related hematologic disorder
- Opportunistic and/or serious infections
- Unanticipated illness or hospitalization deemed related to gene modified cell therapy

A detailed description of the event should include the date of diagnosis and the nature of the diagnosis. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites. If a new malignancy is recorded in a vector target cell type, tumor cells will be evaluated for vector sequences. If the tumor is positive for vector sequences or the surrogate sample is positive for vector sequences and is confirmed in accordance to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled, and submitted within the annual report of the INDs listed on this protocol under which the participant(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 participant(s) evaluated originally received their treatment. Suspected unexpected serious adverse reactions (SUSARs) deemed related to the gene modified cells will be reported to the Regulatory Agencies and shared with Investigators as necessary in the form of Investigator Notification Letters (INL).

7.5 Correlative Studies and Research Assessments

Correlative studies and research assays will be performed during the trial with the aim of monitoring the biological parameters that influence treatment outcome, such as T cell phenotype, function, and persistence of the engineered infused cells, as well as evaluation of candidate biomarkers and their correlation with clinical response to treatment. Data from such studies will be correlated to clinical outcome. These studies will be performed on tumor biopsies, serum and fractionated PBMC plasma samples routinely collected according to the Schedule of Procedures (Table 4). All samples will be processed and/or frozen and analyzed by either central laboratory facilities contracted by the Sponsor or by the Sponsor at the Sponsor's facilities.

Research studies conducted on blood samples may include:

- Flow cytometry to analyze cell subsets and persistence of engineered T cells
- Genomic sequencing to assess T cell clonality through TCR Vbeta and Valpha sequencing and integration site analysis
- Luminex to measure serum cytokine levels

NOTE: As new technologies and data emerge, other assays relevant to the study objectives may be performed.

Biopsy research studies may include:

- Protein, DNA and RNA analysis including PCR and in-situ hybridization to measure infiltration of T cells
- Genomic sequencing to assess T cell clonality through TCR Vbeta and/or Valpha sequencing
- Tissue expression of the target antigen NY-ESO-1 and/or LAGE-1a
- Tissue analysis for immune cell infiltrate and functional biomarkers and gene expression profile
- Tissue analysis to determine the evolution of the mutation profile of the tumor over the course of the therapy

NOTE: As new technologies and data emerge, other assays relevant to the study objectives may be performed

If a subject has an AE, an additional biopsy (for example skin, gastroinstetinal tract, bone marrow, tumor) or blood (serum and PBMC) samples may be requested with the objective of gaining an understanding of the underlying etiology of the AE. For this purpose, the above described research tests may be performed on these samples.

7.5.1 Pharmacogenetics Sample

An optional whole blood sample for pharmacogenetic research may be obtained at any time throughout the study after eligibility is confirmed (refer to Table 4). The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. The blood sample can be taken at Baseline or at any point during the

Interventional Phase of the study provided the subject has given written informed consent for pharmacogenetics research.

Specific genes will be selected from areas of the genome (e.g., candidate genes) including areas associated with mechanisms underlying AEs. The candidate genes that may be investigated in this study include transforming growth factor (TGF)-beta, tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL10 and interferon(IFN)gamma.

7.5.2 Cytokine and Soluble Factors Analysis

Serum is collected at Baseline, and at each visit post infusion up to 12 weeks, to allow for measurement of cytokines in the blood. Serum is also collected from subjects with suspected CRS, with samples being taken approximately every other day until symptoms are improving or an alternative diagnosis is confirmed (refer to Section 8.5). Details regarding serum collection are provided in the Study Procedures Manual.

Cytokines, growth factors and soluble receptors including but not limited to IL-6, IFN-γ, TNF-α, IL-2Rα, IL-10, IL-13, IL-1Ra, IL-8, IL-12, IL-15, IL-2, and GM-CSF are measured .

GLP measurement of the cytokine subset IL-1β, IL-10, IL-6, TNF-α, and IFN-γ is performed. All other measurements are exploratory.

Serum samples may also be used to investigate the presence of antibodies to NY-ESO-1^{c259}T.

7.5.3 Tumor Biopsies

The efficacy of cancer immunotherapy is conditioned by the infiltration of tumors by activated tumor-specific T cells. The activity of these T cells will in turn be affected by the presence in the tumor of an immunosuppressive environment (e.g. regulatory T cells). Therefore, the direct evaluation of the "immune landscape" inside the tumor is of great value for understanding and optimizing cancer immunotherapy. For this reason, core needle biopsies are requested at Screening, Baseline (to evaluate the immune status of the tumor before T cell infusion), Week 8 (at the expected time of an active anti-tumor response by infused T cells), and after disease progression is confirmed, with the exception of subjects for whom there is no safely accessible tumor tissue.

Archival tissue may be used for the screening biopsy, although fresh tissue is preferred. If a fresh biopsy was taken for NY-ESO-1 and/or LAGE-1a confirmation screening in the Screening Protocol (ADP-0000-001), and there is sufficient tumor sample left remaining, this sample may be used as the Baseline sample for these correlative science studies. Otherwise, the baseline biopsy material may be collected anytime between two months and 2 weeks prior to the start of lymphodepleting chemotherapy, 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 >2cm. When possible, the same lesion(s) should be biopsied at both Screening and subsequent time points. The apparent clinical or scan status of the lesion(s) biopsied should be documented at the time (e.g. decreased, stable, increased size or activity).

If feasible, biopsy material should be collected after disease progression has been confirmed and documented, ideally on lesions that have progressed.

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

In subjects who have a pleural effusion or ascites, if there is a clinical requirement for removal of the effusion fluid at any time during the study, collection of samples for GSK translational research studies are requested.

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

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

7.5.4 NY-ESO-1^{c259} TCR^{+} Cell Persistence:

The primary research assays for the trial involve monitoring for the persistence of infused engineered cells in the subjects and for correlation of this with potential therapeutic effect. Persistence is also monitored as a long-term safety measure (refer to Section 10.3). Two well established methodologies will be used to measure the cells:

- Quantitation of NY-ESO-1^{c259} TCR^{+} cells by PCR of transgene from DNA extracted from frozen PBMC
- Quantitation of NY-ESO-1^{c259} TCR^{+} expression cells by flow cytometry from frozen PBMC

7.5.5 NY-ESO-1^{c259} TCR^{+} Cell Phenotype and Activity:

A range of assays will be performed to elucidate the phenotype and activity of the gene-modified T cells (manufactured product) before and after infusion in the blood (and tumor if resection is performed). The assays performed will depend upon availability of sample and clinical / scientific significance. The following assays may be performed:

- Phenotype analysis for determination of T cell lineages
- Quantitation of the senescence and activation status of immune subsets from PBMC
- Quantitation of soluble factors reflecting *in vivo* function of NY-ESO-1^{c259} TCR^{+} T cells
- Anti-gene modified T cell immune responses (tertiary assay).
- *Ex-vivo* activity of transduced cells at different time points to assess potential anergy of those cells.
- Analysis of gene expression profile to reflect activity of the cells

NOTE: Analysis may not be limited to these assays; additional assays may be added as they become available

7.5.6 Liquid Biopsy Collection and Analysis

Recognizing that tumor biopsies cannot always be obtained safely, we set out to investigate whether alternative safer approaches can provide similarly valuable information. Therefore, in addition to tumor biopsies, liquid biopsies (peripheral blood plasma) will be collected in parallel, as well as at other timepoints as listed in the Schedule of Procedures, to extract cell-free DNA (cfDNA) and exosomes to investigate:

- Estimation and genetic profiling of the global tumor burden (including expression of NY-ESO-1 and/or LAGE-1a mRNA and mutational profiling) from exosomes and cfDNA.
- Systemic assessment of the immune response (gene expression by cytotoxic and regulatory immune cells) from exosomes.

7.5.7 Request for Autopsy for Death Following Administration of Gene Transfer Agents

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

8 SUPPORTIVE CARE GUIDANCE

It is recommended that a specialist with experience in the administration of hematopoietic stem cell transplant and/ or other cell and gene therapy be involved in the care of study subjects. All subjects should be hospitalized for the T-cell infusion. Staff treating trial subjects should be experienced in acute post-transplant care and the management of associated toxicities (e.g. cytopenias, CRS, autologous graft versus host disease).

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

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

8.1 T Cell Infusion Symptom Management

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

- Fever, chills, headache and temperature elevations will be managed with acetaminophen. It is recommended 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.

8.2 Infection

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

8.2.1 Pneumocystis carinii Pneumonia

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

8.2.2 Herpes simplex and Varicella zoster

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

8.2.3 Cytomegalovirus

All subjects will be screened for cytomegalovirus (CMV) IgG seropositivity at study entry. If CMV viremia is detected at Baseline, treatment should be initiated with evidence of viral clearance prior to lymphodepleting chemotherapy. All CMV IgG seropositive subjects will continue to be monitored as shown in Table 4 for CMV viremia by CMV DNA PCR until 60 days post infusion of NY-ESO-1^{c259}T cell therapy. In the event CMV viremia is observed, an infectious diseases specialist should be consulted and treatment initiated if necessary according to institutional practice. Recommended regimens include ganciclovir based therapy if ANC ≥1000, and foscarnet if ANC <1000.

If a subject experiences prolonged or secondary pancytopenia or lymphopenia, additional monitoring for viral reactivation should be considered and treatment for viral infection initiated if necessary. A strategy for management of pancytopenia or bone marrow failure is described in Section 8.7.

8.2.4 Hepatitis B Prophylaxis

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

8.2.5 Syphilis

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

8.2.6 Other Anti-Microbial Prophylaxis

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

8.3 Hematologic and Blood Product Support

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

8.3.1 Irradiated Blood Product

Bone marrow suppression can be a consequence of transfusion associated GVHD. To minimize the possibility of transfusion associated GVHD, all blood products transfused within 4 weeks prior to leukapheresis, within 4 weeks prior to initiation of lymphodepleting chemotherapy and following lymphodepleting chemotherapy until at least 6 months following IP infusion or until lymphocyte count returns to $\geq 1.0 \times 10^9$/L (whichever is longer) must be irradiated. In addition, if a subject requires systemic steroids or immunosuppression for the treatment of toxicity, irradiated blood products must be given until recovery of immune function.

8.3.2 CMV Screened Blood Products

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

8.4 Management of Autoimmunity

Subjects should be monitored throughout the trial for potential autoimmune reactions in response to the genetically engineered T cells that could include skin toxicity, liver toxicity, colitis, eye toxicity etc. If autoimmunity is suspected, the Investigator should be contacted and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the NY-ESO-1^{c259}T cell therapy. If the subject sustains persistent Grade 2, or Grade 3 or 4 autoimmunity, consideration should be given to administration of corticosteroid therapy, either topically (e.g. skin, eyes) or systemically as clinically indicated.

8.5 Management of Cytokine Release Syndrome

Cytokine release syndrome is a potentially life-threatening toxicity that has been observed following administration of antibodies and ACTs for cancer. It is defined clinically by symptoms many of which mimic infection, including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash, and dyspnea. 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 caused a rapid rise in serum cytokine levels under conditions of immune activation and although cytokines will be assayed serially throughout the study, results of the assays will not be available in real time; therefore, CRS should be graded and managed with supportive and immunosuppressive interventions according to the severity of symptoms (Lee, 2014).

Table 6 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical, and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection,

cytokine levels as described Section 7.5.2 as well CRP levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 6: Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment	Management Guidelines
1	Temperature ≥38.0 °C	• Vigilant supportive care[1] • Assess for infection and treat[2]
2	Temperature ≥38.0 °C with hypotension not requiring vasopressors and/or hypoxia requiring the use of oxygen delivered by low-flow nasal cannula (≤6 L/minute) or blow-by.	• Monitor cardiac and other organ function • Vigilant supportive care[1] • Assess for infection and treat[2] • Treat hypotension with fluid and pressors • Administer O_2 for hypoxia • Consider administering tocilizumab ±corticosteroids[3]
3	Symptoms require and respond to aggressive intervention hypotension requires multiple pressors or high dose pressors hypoxia requires ≥40% O^2, Grade 3 organ toxicity or Grade 4 transaminitis	• Monitor subject very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). • Vigilant supportive care[1] • Assess for infection and treat[2] • Treat hypotension with fluid and pressors. Administer O_2 for hypoxia. • Administer tocilizumab± corticosteroids[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 tocilizumab± corticosteroids[3]
5	Death	

1. Fever is defined as temperature _38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
3. Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.
4. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure
5. 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.
6. Given that prolonged fluid resuscitation without pressor use is associated with worse outcome and because early and aggressive supportive care, early use of vasopressors, and timely anti-cytokine therapy are paramount to

mitigating life-threatening CRS.
7. Other immunosuppressor agents may be used, including TNFα and IL-1R inhibitors
Source: (Lee, 2019)

Grade 1 CRS is defined as fever (≥38.0°C) with or without constitutional symptoms (Table 6). The constitutional symptoms of CRS, such as myalgia, arthralgia, and malaise, are by themselves nonspecific; however, when coincident with fever in the expected timeframe, the etiology of CRS is more likely.

Grade 2 CRS is defined as fever (≥38.0°C) with hypotension not requiring vasopressors and/or hypoxia requiring the use of oxygen delivered by low-flow nasal cannula (≤6 L/minute) or blow-by (Table 6).

Grade 3 CRS is defined as fever (≥38.0°C) with hypotension requiring 1 vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula (>6 L/minute), facemask, nonrebreather mask, or venturi mask not attributable to any other cause (Table 6).

Grade 4 CRS is defined as fever (≥38.0°C) with hypotension requiring multiple vasopressors (excluding vasopressin) and/ or hypoxia requiring positive pressure [eg, Continuous airway positive pressure (CPAP), bilevel positive airway pressure, intubation, mechanical ventilation] not attributable to any other cause. Outside of vasopressin, adding a second agent is a strong indication that the patient remains hemodynamically unstable after the first intervention. Such a scenario would be consistent with grade 4 CRS. Any use of positive-pressure ventilation constitutes a grade 4 CRS. Intubation of a patient without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not, by definition, grade 4 CRS. By extension, a patient experiencing seizures in which a compromised airway affects oxygenation and intubation reverses such deficits is not considered to have grade 4 CRS, because the seizure rather than CRS is the cause of the hypoxia. Furthermore, a patient who remains intubated for a neurologic cause is not considered to have CRS when the other signs of CRS have resolved.

By convention, grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome.

Subjects requiring immunosuppressive intervention may receive tocilizumab, steroids, or both (Davila, 2014; Lee, 2014; Lee 2019). Tocilizumab is a humanized anti-IL-6 receptor antibody that has been used to manage severe CRS (although it is not approved for this indication).

Anecdotally, tocilizumab has produced rapid and complete correction of CRS with single doses (Maude, 2014). Lee et al., recommended administration of tocilizumab 4mg/kg administered over 1 hour in adult subjects as the first-line treatment of severe CRS. Subjects may receive a repeat dose if clinical signs and symptoms do not improve within 24-48 hours.

Side effects attributed to chronic use of tocilizumab in rheumatologic disease include transaminitis, thrombocytopenia, elevated cholesterol and low-density lipoproteins, neutropenia and increased infections but acute infusional toxicities have not been reported in CRS use (Lee, 2014; Lee, 2019).

Subjects unresponsive to tocilizumab or experiencing severe neurological symptoms (e.g. confusion, delirium, seizure, etc.) may require treatment with steroids. Lee et al. [Lee, 2014; Lee, 2019], recommend steroids as second-line therapy for CRS as the response to

tocilizumab may be more rapid and owing to the potential of steroids to attenuate the anti-tumor effects of the ACT. However, in subjects with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability or other life-threatening symptomatology, consideration may be given to the use of corticosteroids as a preferred first-line immunosuppressive therapy. High doses (e.g. 2 mg/kg/day prednisone equivalent) may be required.

If CRS is suspected, a physician with expertise in the management of subjects following bone marrow transplant should be consulted. If high-dose corticosteroids are required, treatment should generally be continued for at least 5 days followed by tapering doses over several weeks.

Please refer to the most recent version of the product label for tocilizumab.

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

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

8.6.1 Diagnosis of GVHD

The diagnosis of GVHD is predominantly based on clinical findings and is often one of exclusion (Table 7). Many of these symptoms can also occur in the setting of the preparative regimen, high dose cyclophosphamide as well as with CRS. Any of these conditions including GVHD can be associated with fever. The skin is the most commonly involved organ, followed by the gastrointestinal 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 7: Overview of Clinical Findings/Symptoms of GVHD

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

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

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

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

8.6.2 Grading of GVHD

Grading of acute GVHD is based on the stage of dermal, gastrointestinal, and hepatic involvement as described in Table 8 . Careful measurement of stool volume and assessment of percentage of body area covered by rash are important for proper grading and treatment.

Table 8: Staging of Dermal, Gastrointestinal and Hepatic Involvement with Acute GVHD

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

With the addition of assessment of functional impairment, grading can be determined using Table 9 (Glucksberg, 1974).

Table 9: Grading of Acute GVHD

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

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

8.6.3 Management of GVHD

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

If GVHD is suspected:

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

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

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

General guidelines for first-line treatment based on grade are provided in Table 10, and should be considered in conjunction with input from the consulting physician with bone marrow transplant expertise.

Table 10: Management Guidelines for GVHD

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

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

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

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

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

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

8.7 Management of Pancytopenia with Bone Marrow Failure / Aplastic Anemia

Pancytopenia with bone marrow failure / aplastic anemia has been reported after initial bone marrow recovery from high-dose chemotherapy followed by infusion of NY-ESO-1^{c259}T-cells. Bone marrow recovery following lymphodepletion will be defined as:

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

Aplastic anemia is a rare hematological disorder characterized by pancytopenia and a hypocellular marrow. Subjects are usually symptomatic on presentation but some are detected incidentally when unexpected cytopenias are found on a routine blood count. The

diagnosis of severe aplastic anemia is made in the setting of a hypocellular bone marrow when 2 of the following 3 blood counts are met: ANC <500/μL, absolute reticulocyte count <60,000/μL, and platelet count <20,000/μL, and myelodysplastic syndrome is ruled out. The clinical consequences of aplastic anemia are life-threatening bleeding from thrombocytopenia, and infection as a result of neutropenia. Bacterial and fungal infections are common and a significant cause of morbidity and mortality.

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

- Consult a physician with expertise in the management of aplastic anemia
- Increase the frequency of CBCs as clinically indicated.
- Exclude other alternative etiologies such as other drugs, viral causes, etc.
- An early bone marrow biopsy is recommended for clinical diagnosis, with a sample to be provided to the Sponsor for study. Details on tissue collections, kit use and shipment information can be found in the SPM and refer to Section 7.5.
- A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the Sponsor. Refer to Section 7.5.
- Initiate treatment with G-CSF
- Consult an Infectious Diseases expert
- Once alternative etiologies have been excluded, strongly consider immunosuppression (e.g. methylprednisolone 2mg/kg initial dose) or more aggressive regimens (e.g. antithymocyte globulin (ATG), cyclosporine, eltrombopag) as well as antimicrobial prophylaxis/therapy with the advice of your hematology/Infectious Diseases consultant(s). If high dose corticosteroids are initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

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

8.8 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 product labels. Refer to the most current product labels, and Section 6.1 for details of prohibited medications.

8.8.1 Management of Neutropenia

The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF is recommended in all subjects. G-CSF (e.g., filgrastim) should be used for management of neutropenia according to ASCO guidelines (Smith, 2015). G-CSF should be should be given starting 24 hours after the

administration of chemotherapy 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 24 hours post the final dose of cyclophosphamide.

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

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

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

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. ICANS may occur with other cancer immunotherapies, including TCRs. Cancer patients may also be at risk for ICANS 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.

8.9.1 Management of ICANS

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

Grade 1 ICANS is primarily managed with supportive care as outlined below. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first line treatment of for ICANS in the setting of CRS. 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 all subjects with ICANS for thorough

neurological evaluation, and recommendations for further testing such as electroencephalogram (EEG) and neuroimaging as indicated.

Table 11: Management of ICANS

ICANS Grade	Treatment
1	• 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 • Neurology consultation including fundoscopic exam to assess for papilloedema • 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 of the 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] IVor 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 • Consider Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h if refractory to anti-IL-6 therapy, or for ICANS without concurrent CRS; 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 papilloedema with cerebrospinal fluid (CSF) opening pressure <20 mmHg should be treated corticosteroid regimen as per Grade 4 below. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 ICANS
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 800 mg

Grade 1 ICANS. Grade 1 ICANS is defined as a score of 7-9 on the ICE assessment (**Table *8***). A patient with grade 1 ICANS may have a delay in responses or disorientation to time or place, mild inattention with difficulty in counting numbers backwards, or impairment of handwriting. There may be drowsiness, but

patients awaken spontaneously, and when prompted, the patient should be able to complete most of the ICE assessment. Grade 1 ICANS may be seen during CRS waxing and waning with febrile episodes.

Grade 2 ICANS. Grade 2 ICANS is defined as a score of 3-6 on the ICE assessment (**Table *8***). Expressive aphasia is the most specific first sign of severe neurotoxicity and early signs during grade 2 include paraphasic errors (the production of unintended syllables and words during attempts to speak) and verbal perseveration with patients repeating the same words over and over. Patients with grade 2 ICANS are able to communicate their needs but it is effortful. Patients may have depressed level of consciousness but are arousable to voice and the responses may be slowed.

Grade 3 ICANS. Grade 3 ICANS is defined as a score of 0-2 on the ICE assessment (**Table *8***). Patients with grade 3 ICANS have severe global aphasia and are not speaking or following commands even when wide awake and therefore may be unable to complete any of the ICE questions. Alternatively, they may have excessive drowsiness and need tactile stimulus to attend to examiner. Any clinical seizure whether simple partial, complex partial or generalized, and any electrographic seizures would also meet criteria for grade 3 ICANS (Table 12, Table 13). If neuroimaging shows new focal or local edema this would also be categorized as grade 3 ICANS (Table 12, Table 13). However, intracranial hemorrhage due to coagulopathy or other causes with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.

Grade 4 ICANS. Grade 4 ICANS is defined as patients who have a score of 0 on the ICE assessment (**Table *8***) due to being unarousable and unable to perform the ICE assessment. Stupor and coma may be seen; the stuporous patient only responds by grimacing or drawing away from vigorous or repetitive tactile stimuli and the comatose patient is unarousable and/or unresponsive. This depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication), which is often a complicating factor in sick patients with CRS. Some patients may require intubation for airway protection. In addition, any patient having prolonged or repetitive clinical or subclinical electrographic seizures without return to baseline in between, or deep focal motor weakness such as hemiparesis or paraparesis would be considered to have Grade 4 ICANS. Patients with symptoms and signs of elevated ICP such as projectile vomiting with headache, depressed consciousness, cranial nerve VI palsies, papilledema, Cushing's triad of bradycardia, hypertension and respiratory depression, decerebrate or decorticate posturing, or diffuse cerebral edema on head imaging would also be considered to have grade 4 ICANS.

Grade 5 ICANS. By convention, Grade 5 ICANS is defined as death due to ICANS where another cause is not the principle factor leading to this outcome.

8.9.2 Monitoring for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Brain MRI (or CT Scan if MRI not feasible) should be obtained in all subjects at the time of screening. Baseline brain MRI should be repeated if more than 4 months have elapsed prior to lymphodepletion.

ICE should be measured on the day of NY-ESO-1^{c259}T cell infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following NY-ESO-1^{c259}T cell infusion. If a subject is found to haveICANS, the ICEshould be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

8.9.3 Grading of ICANS

[Lee, 2019] have developed a new grading system for ICAN which incorporates use of a

modified version of the CARTOX 10-point neurological assessment termed Immune Effector Cell-Associated Encephalopathy (ICE) tool, see Table 12. Points are assigned for each of the tasks in Table 12 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. The ICE score is used in grading of ES as presented in Table 28.

Table 12: Immune Effector Cell-Associated Encephalopathy (ICE) assessment tool

Task	ICE Points
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

Scoring: 10, no impairment; 7-9; grade 1 ICANS; 3-6, grade 2 ICANS; 0-2, grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

The ICE score is used in grading of ICANS as presented in Table 13.

Table 13: Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)Encephalopathy Syndrome

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.			
Depressed level of consiousness[2]				
Elevated ICP/ cerebral edema				

Motor findings[5]	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
Seizure	

ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICP = Intracranial Pressure; N/A = not applicable.

1. See Table 12 for ICE. 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 (eg, no sedating medication)
3. Papilloedema grading is performed according to the modified Frisén scale.
4. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.
5. Tremors and myoclonus associated with immune effector cell therapies do not influence ICANS grading.
This table is based on Lee, 2019.

8.9.4 Monitoring for ICANS

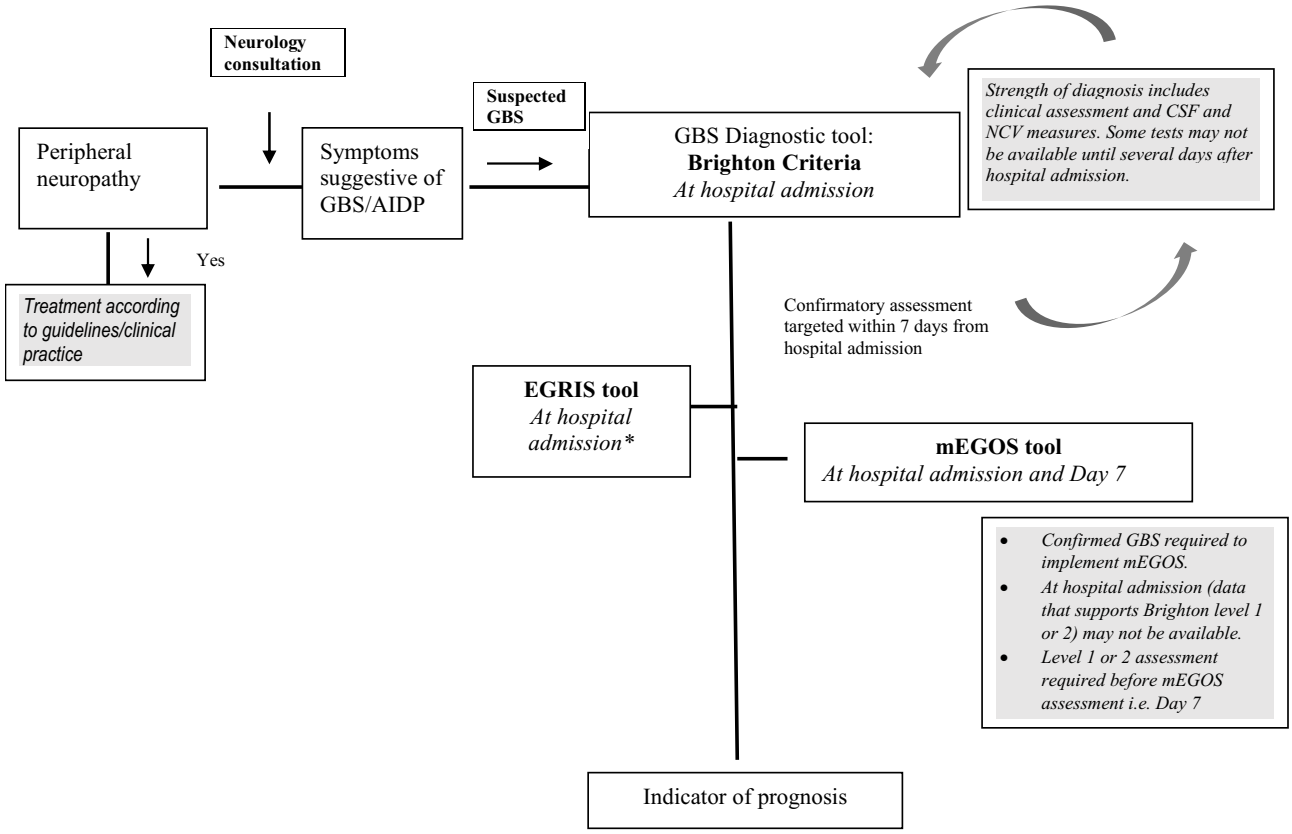
Brain MRI (or CT Scan if MRI not feasible) should be obtained for all participants at the time of screening. Baseline brain MRI should be obtained within 4 weeks prior to lymphodepletion.

ICE should be measured on the day of NY-ESO-1^{c259}T infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. If a participant is found 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.

8.10 Management of Guillain-Barré Syndrome (GBS)

Please obtain a neurology consultation for all participants with signs or symptoms suggestive of GBS for thorough neurological evaluation, and for expert recommendations on further diagnostic workup including EMG, lumbar puncture, infectious panel to guide management and follow up.

Case assessment for possible Guillain Barre Syndrome using diagnostic and prognostic tools supported by medical diagnosis and/or medical treatment



**Please refer to algorithm for treatment described in Figure 2.*

8.10.1 Neurological Symptoms

The following features should be considered as suggestive of a GBS diagnosis in clinical practice and the use of the Brighton criteria [Fokke, 2014] together with further neurological evaluation will be the basis for confirmation of diagnosis:

Progressive weakness in legs and arms (sometimes initially only in legs)

- Areflexia (or decreased tendon reflexes) in weak limbs

Additional symptoms

- Progressive weakness phase lasts 2 to 4 weeks (often 2 weeks)
- Relative symmetry of weakness
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction

- Pain

8.10.2 Brighton Key Diagnostic Criteria

At admission and confirmation within 7 days of admission:

- Bilateral and flaccid weakness of limbs
- Decreased or absent deep tendon reflexes in weak limbs
- Monophasic course and time between onset – nadir 12 hours to 28 days
- CSF cell count < 50/µl
- CSF protein concentration > normal value
- Nerve conduction studies findings consistent with one of the subtypes of GBS
- Absence of alternative diagnosis for weakness

8.10.3 Erasmus GBS Respiratory Insufficiency Score (EGRIS)

Probability of acute risk first week following hospital admission of respiratory insufficiency [Walgaard, 2010].

Parameters required at hospital admission:

- Days between onset of weakness and admission
- Facial and/or bulbar weakness at admission
- Medical Research Council sum score

8.10.4 Modified Erasmus GBS Outcomes Score (mEGOS)

Parameters required at hospital admission and 7 days later [Walgaard, 2011]:

- Age at onset
- Preceding diarrhoea (in 4 weeks preceding onset of weakness)
- Medical Research Council sum score

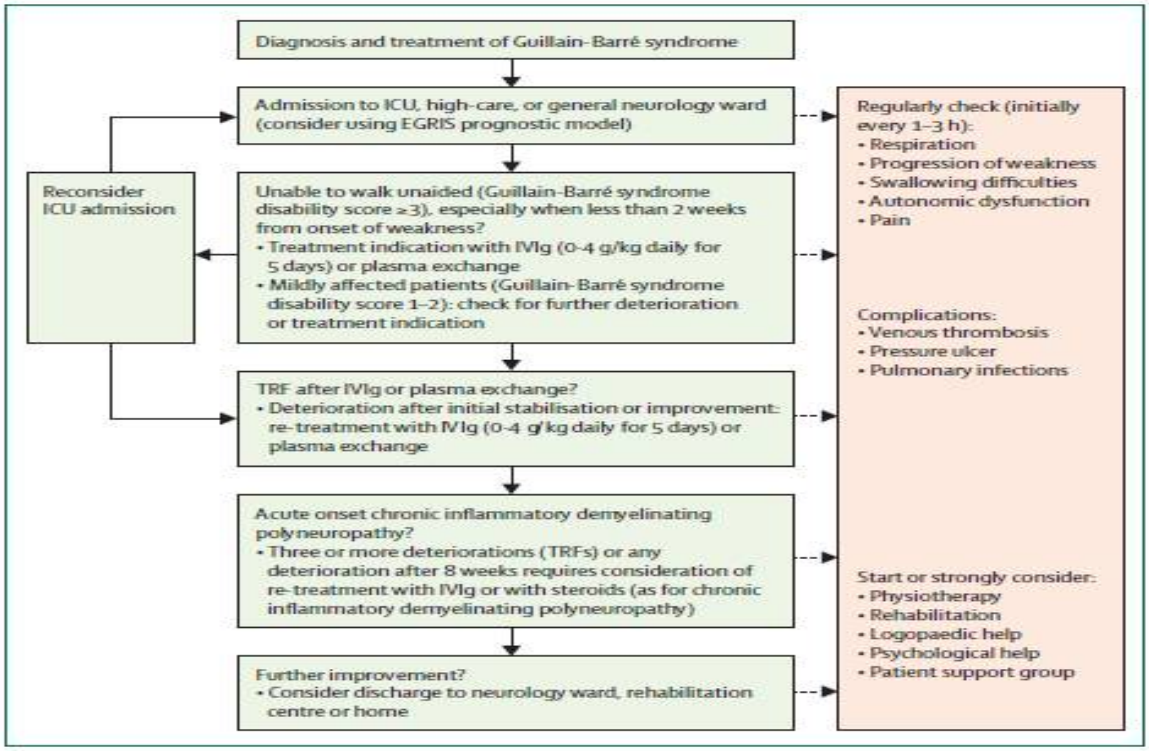
Summary of diagnosis and treatment for GBS

Additional information on the diagnosis and management of GBS (Figure 2) can be found in a review article on GBS [Willison, 2016].

8.10.5 Summary of diagnosis and treatment for GBS

Additional information on the diagnosis and management of GBS (Figure 2) can be found in a review article on GBS [Willison, 2016].

Figure 2 Diagnosis and Treatment of Guillain-Barré Syndrome (GBS)



Abbreviations: EGRIS = Erasmus GBS Respiratory Insufficiency Score; GBS = Guillain-Barré Syndrome; ICU = intensive care unit; IVIg = intravenous immunoglobulin; TRF = treatment related fluctuation.
Source with permission: Willison, 2016.

9 RECORDING ADVERSE EVENTS

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

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

9.1 Time Period for Collecting AE and SAE Information

AEs and SAEs will be collected at the time points specified in the Schedule of Procedures (Table 4) and as described herein:

- SAEs or AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or leading to early withdrawal will be collected in the AE section of the CRF from the time a participant signs the informed consent form until leukapheresis. All other relevant events that begin before the start of leukapheresis but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section..
- From leukapheresis until the lymphodepletion, all SAEs and other reportable safety events that could affect patient eligibility or study participation (e.g., protocol-specified intervention, including but not limited to, wash-out or discontinuation of usual therapy, diet, or a procedure) will be collected.
- All AEs and SAEs will be collected from the start of lymphodepleting chemotherapy until the end of the study. Refer to Section 9.4 for details on emerging clinical conditions that must be reported post-infusion.
- All SAEs have to be reported to Sponsor within 24 h of Investigator learning about them.
- All pregnancies and exposure during breastfeeding, from the start of chemotherapy (lymphodepletion regimen) through the contraception period (see Section 9.8) must be reported by the Investigator.
- Additionally, any SAE brought to the attention of an Investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.
- AEs and SAEs occurring after the participant rolls over to the LTFU study (GSK Study 208750) will be collected and reported in the LTFU protocol database.
- During LTFU for subjects who do not enroll in the LTFU study, subjects will only be monitored for those emerging clinical conditions defined in Section 9.4.

9.2 Definition of Adverse Event

In accordance with the ICH, an AE is any untoward medical occurrence in a subject or clinical investigation subject who receives a pharmaceutical product, regardless of causality. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during the study are to be reported as AEs. For guidance on reporting laboratory test abnormalities as AEs, refer to Section 9.10.

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

All AEs should be followed until:

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

On completion of the subject from the Interventional Phase of the study, or withdrawal from the study, serious or severe AEs will be followed until one of the above criteria is met. SAEs related to NY-ESO 1^{c259}T will continue to be recorded and monitored into long-term follow-up (refer to Section 9.4).

9.2.1 Assessment of Intensity

AEs will be graded according to the CTCAE v 4.0. The Investigator will assess intensity of all AEs using this five point scale (Grade 1-5) and record on the eCRF.

AEs not specifically listed on the CTCAE should be graded according to Table 14:

Table 14: Grading of AEs Not Specified in CTCAE v4.0

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

9.2.2 Assessment of Causality

The Investigator will assess the causal relationship between the AE and NY-ESO-1^{c259}T product according to his/her best clinical judgement. An assessment of possibly/probably/definitely related is meant to convey there is evidence of a causal relationship, not that a relationship cannot be ruled out. The Investigator should consider alternative causes such as natural history of the underlying disease, lymphodepleting chemotherapy, concomitant medications and other risk factors when making an assessment. The following scale will be used as guidance:

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

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

9.3 Reporting Serious Adverse Events (SAEs)

An SAE is any AE that:

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

Medical and scientific judgment should be exercised in deciding if an AE is of significant enough medical importance to be classified as serious outside the above definitions. Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require

intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious. In this case event will be reported using the serious criteria of clinically significant or requires intervention.

Additional protocol-defined criteria

- Any Grade ≥3 cytokine release syndrome or GVHD, and all cases of Guillain-Barré syndrome or acute demyelinating neuropathy must be reported as an SAE within 24 hours (Section 9.6).

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

All SAEs have to be reported to Sponsor within 24 h of Investigator learning about them.An SAE must be recorded by completing the SAE eCRF form within EDC systemIn addition, an SAE Worksheet must be completed and submitted to GSK within 24 hours by e-mail to PPD and PPD (or fax:PPD).

NOTE: The SAE eCRF within the EDC system is the primary method for reporting SAEs. The SAE Worksheet should only be used if the EDC system is unavailable.

The SAE eCRF must be completed by the Investigator with as much information as is available. The minimum reporting criteria include:

- Identifiable subject (Subject ID)
- Serious adverse event
- Suspect investigational product
- Identifiable reporting source (PI acknowledgment of the report and signature are required)
- Relationship to investigational product.

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

Please refer to the SPM for the back-up SAE Worksheet.

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

Due to the nature of the treatment, subjects are required to be followed for up to 15 years after treatment with genetically modified T cells for observation of delayed AEs according to FDA and EMA guidance (FDA, 2006a; FDA, 2010; EMEA, 2009). Subjects with delayed AEs will be followed until disease progression and then will continue to be monitored in the LTFU protocol. 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

- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of an immune-related hematologic disorder
- Serious infections (including opportunistic)
- Unanticipated illness or hospitalization deemed related to gene modified cell therapy

A detailed description of the event should include the date of diagnosis and the nature of the diagnosis. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites. If a new malignancy is recorded in a vector target cell type, tumor cells will be evaluated for vector sequences. If the tumor is positive for vector sequences or the surrogate sample is positive for vector sequences and is confirmed in accordance to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled, and submitted within the annual report of the Investigational New Drugs (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. Suspected unexpected serious adverse reactions (SUSARs) deemed related to the gene modified cells will be reported to the Regulatory Agencies and shared with Investigators as necessary in the form of Investigational new drug safety reports (INDSRs).

All the above listed AEs should be followed until:

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

9.5 Progression of Underlying Malignancy

Progression of underlying malignancy and related symptoms are not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

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

9.6 Regulatory Reporting Requirements for SAEs

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

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

An Investigator who receives an INDSR describing a SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from GSK will file it with the IB and notify their IRB/IEC if appropriate, in accordance with local requirements.

On request of a Competent Authority in whose territory the clinical trial is being conducted, the Sponsor will submit detailed records of all AEs which are reported to him by the relevant Investigator(s).

9.7 Cardiovascular and Death Events

For any cardiovascular events detailed below and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary of Regulatory Activites (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

9.8 Pregnancy

There is no pre-clinical or clinical trial data of NY-ESO-1^{c256}T in pregnant women; however, there is a reasonable but unproven likelihood that this intervention may be significantly embryotoxic or even an abortifacient given the underlying biology of the target. The effects on breast milk are unknown; therefore, breastfeeding should be discontinued for the duration of the study starting at the first dose of chemotherapy and for at least 12 months after receiving the investigational product, or 4 months after there is no evidence of persistence/gene modified cells in the subject's blood, whichever is longer.

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

If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy.

9.9 Pre-existing Condition

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

9.10 Laboratory Test Abnormalities as Adverse Events

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

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

9.11 Timelines for Safety Reporting

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 Hours	Pregnancy Notification Form	2 Weeks	Pregnancy Followup- Form

10 SAFETY MONITORING

10.1 Safety Review Team

A SRT will be implemented in this study. In line with routine pharmacovigilance, a GSK SRT will review blinded safety data, including clinical laboratory parameters and AEs, at appropriate intervals during the period of study conduct. Recommendations on study modification, halting the study and/or pausing enrollment will be provided by the SRT. A SRT charter, defining roles and accountabilities and the process for safety review and meeting frequency, will be available.

10.2 Mandated Study Pause Due to GBS

The occurrence of any event of GBS will mandate a pause in enrollment and stopping treatment for all participant within the GSK3377794 studies. The case must be diagnosed by a neurologist as GBS according to diagnostic guidance for GBS [Fokke, 2014].

10.3 Monitoring and Management of Replication-Competent Lentivirus (RCL)

Replication competent lentivirus (RCL) is a theoretical risk associated with the use of lentiviral vectors; no RCL has ever been detected in vitro or in vivo. The risk is derived from the detection of replication competent retrovirus (RCR) during the use of early γ retroviral vector packaging systems which were inadequately designed to avoid recombination events between the vector and packaging components (Miller, 1990). Updated γ retroviral packaging systems have not been associated with RCR. However in a study with Rhesus monkeys, three out of 10 animal died of lymphomas at around 6 months after transplantation of vector transduced bone marrow cells contaminated with replication-competent virus (Donahue, 1992). Therefore, RCR/L must continue to be rigorously evaluated in vector and cell lots, and in subjects post infusion with any product involving a retrovirus (FDA, 2006a; FDA, 2006b; FDA, 2010; EMEA, 2009).

A RCL may be generated during the production phase or subsequently after introduction of vector transduced cells into the subject. RCL may be generated between homologous or non-homologous recombination between the transfer vector and packaging elements, or endogenous retroviral elements (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 a RCL by recombination with an endogenous virus (i.e., HIV) in the subject following infusion of the vector product remains a theoretical possibility. The consequences of such recombination events could be neutral, could reduce the replication rate or pathogenicity of the subject's virus, or could increase the replication rate or pathogenicity of the subject's virus. Since the development of a strain with increased pathogenicity would pose greater risk to both the subject and their close contact(s), periodic monitoring for RCL is conducted during the course of the trial and during the 15 year follow up.

Regulatory Agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject (FDA, 2006a; FDA, 2006b; EMEA, 2009). However, because the probability and characteristics of an RCL are unknown, no concrete plans have been put in place. As of the writing of this protocol, it is agreed that the subject must be isolated and no additional subjects treated with NY-ESO-1^{c259}T cells until an action plan is agreed upon as outlined in Section 10.5.

The following approaches have been discussed for subject management:

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

10.4 Testing for RCL in Clinical Studies

RCL will be monitored using a PCR-based assay that detects and measures copies of the gene coding for the vector's envelope protein, namely Vesicular Stomatitis Virus G protein (VSV-G) that is necessary for the assembly of pseudotyped infectious lentiviral particles but absent from the vector's backbone. RCL testing and monitoring will take place on:

- The cell product, whereby RCL testing will be performed by or under the direction of the manufacturing facility responsible for manufacturing and release of the vector.
- Subject PBMCs will be collected prior to infusion of transduced T cells and then at 3, 6, and 12 months post treatment. If these tests are negative at all time points during the first year, PBMC samples will be collected annually until assessments for persistence have discontinued (Section 10.7) or until Year 15, whichever comes first. Samples will be archived at GSK's centralized biorepository.
- If VSV-G DNA copies are detected at any time point in the first year post-infusion, the safety monitoring protocol (Section 10.5) will be triggered. 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, then subject samples will be collected annually until year 15 and archived at GSK's centralized biomarker repository or until assessments for persistence have discontinued (Section 10.7).

10.5 Safety Monitoring Results

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

If the second test is positive, infusions for all subjects receiving cells modified with the same vector lot will be postponed. The subject with the confirmed positive VSV G signal will be scheduled for leukapheresis and a biological RCL performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product (Manilla, 2005).

If the biological RCL is positive, all NY-ESO-1^{c259}T cell infusions will be halted. An action plan will be discussed with FDA and other Regulatory Authorities and experts as appropriate. Additional subjects will not be treated until such time as a plan is agreed upon, completed, and reviewed.

10.6 Persistence Testing and Monitoring for Insertional Oncogenesis

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidance's (FDA, 2006a; FDA, 2006b; EMEA, 2009). Insertional oncogenesis is a theoretical risk in T cells transduced with a lentiviral vector. T cells appear resistant to transformation by integrating viruses (Cattoglio, 2010; Newrzela, 2008). However, there are cases of oncogenesis with γ-retroviral transduced stem cells. Four of nine subjects with X-linked severe combined immunodeficiency (SCID-X1) treated with retrovirus transduced stem cells were found to have insertion near the LMO2 proto-oncogene promoter, leading to aberrant transcription and expression of LMO2 which resulted in acute T-cell lymphoblastic leukemia (Hacein-Bey-Abina, 2003; Hacien-Bey-Abina, 2014). Additionally, two subjects

treated for X-linked chronic granulomatous disease (X-CGD) with retroviral transduced stem cells demonstrated insertional activation of the EVI1 transcription factor which resulted in genetic instability, monosomy 7 and clonal progression toward myelodysplasia (Stein, 2010).

10.7 Testing for Persistence of Gene Marked Cells in Clinical Studies

Peripheral blood mononuclear cell samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects prior to infusion of transduced T cells and at 3, 6 and 12 months post-infusion, then every 6 months until 5 years post-infusion and every year from year 6 to 15 post infusion in accordance with the FDA and EMA guidance's (FDA, 2006a; FDA, 2006b; EMEA, 2009). The samples will be tested using a PCR-based method to detect the presence of the Psi gene, which is part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion greater than 1% PBMCs test positive for the vector sequence, the subject's PBMCs will be evaluated for integration site analysis (see Section 10.8). If no gene modified cells are detected for three consecutive assessments post-infusion, and the subject is ≥5 years post-infusion (for example, negative persistence assessments at year 4, 4.5 and 5), no further monitoring of PBMCs is required and collection of samples for persistence may be discontinued. All other laboratory assessments such as RCL, hematology and chemistry may also be discontinued. Subject will continue to be followed by the Investigator by phone call or survey for up to 15 years post-infusion. The Investigator will be the primary physician responsible for continued follow up of the subject for the duration of LTFU, whenever possible. If contact with the Investigator becomes no longer feasible, follow up can be transitioned to a local physician, preferably an oncologist.

10.8 Testing for Insertional Oncogenesis

If persistence, as detected by the presence of a vector sequence (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 sequencing for integration site analysis. Integration site analysis assesses clonality and the possibility of insertional oncogenesis. This integration site analysis method, used in previous clinical trials (Hacein-Bay, 2015), uses sonic length quantitation, an accurate method of measuring relative clonal abundance (Berry, 2012).

If there is clonal dominance in the genetically modified T cell population (either monoclonality or oligoclonality) the persistence assessment will be repeated within 3 months on a new sample. If the repeated analysis demonstrates: 1) persistent monoclonality, 2) evidence of insertional oncogenesis or 3) clonal expansion (an increase in percent predominance of a clone), there will be a review by the Sponsor to develop a monitoring plan specific to the health care risk, and strategies to inform appropriate subjects, investigators, FDA, and other regulators of the findings.

If the integration site analysis indicates polyclonality of the genetically modified T cell population, then screening will continue as scheduled.

10.9 Monitoring and management for Demyelinating Neuropathy and other Neurological events

Obtain a neurological consultation for participants with Grade 2 or higher neurologic events of a ≥ 7 day duration. Participants who develop signs and symptoms consistent with GBS must be evaluated by a neurologist to provide expert recommendations to guide appropriate diagnostic workup such as EMG, lumbar puncture, infectious panel to guide management and follow up.

11. STATISTICAL AND DATA ANALYSIS

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

11.1 Study Populations

Intent-to-Treat (ITT) population: all participants who were enrolled in the trial and met all eligibility criteria.The ITT population is the primary population for the safety of the end-to-end autologous T cell therapy procedure.

Modified Intent-to-Treat (mITT) population: all subjects in the ITT population who receive at least one NY-ESO-1^{c259}T cell infusion.

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

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

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

11.2 Sample Size Calculations

Ten (10) subjects are planned for treatment with NY-ESO 1^{c259} T. The sample size in this study has been based on clinical judgement. This is a small pilot study to describe the safety and tolerability where efficacy endpoints are secondary and will be summarized using estimation methods such as exact 95% confidence intervals. The study is not powered to conduct statistical hypothesis testing.

11.3 Interim Analyses

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

11.4 Statistical Methods for Safety Endpoints

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

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

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

Vital Signs – Vital signs will be listed and reviewed for each subject. Depending on the size and the scope of changes, summaries of vital signs data over time and/or changes from day 1 pre-dose value over time may be provided.

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

Anti-NY-ESO-1^{c259}T Antibodies– The subject incidence of anti-NY-ESO-1^{c259}T antibody formation will be computed and the anti- NY-ESO-1^{c259}T antibody results will be listed.

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

Clinical Laboratory Tests– Clinical chemistry, hematology, and urinalysis data will be listed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Laboratory abnormalities will be graded using CTCAE version 4. Each subject's maximum post-Baseline grade will be computed for each laboratory parameter and referred to as their worst grade for that laboratory parameter. For each parameter shift tables from Baseline to worst grade may be presented.

11.5 Statistical Methods for Efficacy Endpoints

To determine the effect of the treatment of NY-ESO-1^{c259}T cell infusion on tumor response and progression, summaries of efficacy will be based ORR; best overall response; time to and duration of response; duration of stable disease; PFS; and OS. Details will be described in the RAP.

The primary efficacy endpoint is ORR defined as the proportion of subjects with a confirmed CR or PR per RECIST v1.1 relative to the total number of subjects in the corresponding analysis population. The ORR will be based on confirmed responses from the Investigator assessment of overall response. The 95% exact confidence intervals (CI) for ORR will be calculated.

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

Disease Control Rate (DCR), defined as the percentage of participants with a confirmed SD or better as the BOR (i.e., PR, CR, or SD ≥12 weeks), as assessed by the investigator per RECIST 1.1 Criteria.

In addition, PFS, defined as the interval between the date of T-cell infusion day and the earliest date of disease progression or death due to any cause, and PFS will be summarized using Kaplan-Meier Product Limit Method for quartile estimates if data warrant.

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

12. CLINICAL SUPPLIES

12.1 Packaging and Labelling

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

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

12.2 Standard Policies and Product Return

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

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

12.3 Storage and Handling

The subject's T cell product received at the site from the manufacturer will be stored below —135°C until being ordered by the Investigator (or designee) to be infused. The cells will be thawed and infused as specified in Section 5.3.

12.4 Product Accountability

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

- Deliveries of the investigational product are correctly received by a responsible person
- Such deliveries are recorded
- Investigational product is handled and stored safely and properly as stated on the label
- Investigational product is only dispensed to study subjects in accordance with the protocol

- Any unused product is accounted for in the site's records before returning to the Sponsor (or designee)

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

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management

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

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

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

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

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

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

13.2 Case Report Forms

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

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

13.3 Source Documents and Background Data

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents are classified into two different 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, signed informed consents. In no case is the eCRF to be considered as source data for this trial.

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

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

13.4 Data Retention and Availability

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

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

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

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

14. STUDY MONITORING

Study Monitoring will be completed 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 the various records of the trial (e.g., eCRFs ISF, and source documents) provided that subject confidentiality is maintained in accordance with local requirements.

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

14.1 Audit and Inspections

The Sponsor or its representatives may conduct audits at investigative sites including, but not limited to, facilities where the study is being conducted, investigational product handling and

accountability, presence of required documents, the informed consent process and comparison of eCRFs with source documents.

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

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

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

15. REGULATORY AND ETHICAL CONSIDERATIONS

15.1 Competent Authority Submissions

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

15.2 Independent Ethics Committees

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

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

15.3 Local Regulations/ Declaration of Helsinki

The Investigator will ensure this study is conducted in full compliance with the principals of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever, affords the greater protections to the subject. The study must fully adhere to the principles outlined in "Guideline for Good Clinical practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the subject.

15.4 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study related procedures being performed. All consent documentation must be in accordance with applicable regulations and ICH GCP. Documentation must include the dated signature of both the subject (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.

15.5 Confidentiality

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

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

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

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

15.6 Protocol Adherence

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

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

15.7 Completion of the Study and Study Termination

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

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

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

15.8 Public Posting of Study Information

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

15.9 Clinical Study Report

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

15.10 Publication Policy

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

16. APPENDICES

APPENDIX 1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviations and Specialist Terms

ACT	Adoptive T cell Therapy
AE	Adverse Event
ALK	Anaplastic lymphoma kinase receptor
ALT	Alanine amintransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATG	Antithymocyte globulin
CAR	Chimeric antigen receptor
cfDNA	Cell-free DNA
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DCR	Disease Control Rate
DLCO	Diffusing capacity of the lungs for carbon monoxide
DNA	Deoxyribonucleic acid
DSUR	Developmental Safety Update Report
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediamineteraacetic acid
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMG	Electromyography
FDA	Food and Drug Administration
FDG-PET	18-fluorodeoxyglucose positron emission tomography
FEV1	Forced expiratory volume in 1 second

FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GGTP	Gamma glutamyl transpeptidase
GVHD	Graft-Versus-Host Disease
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
HTLV	Human lymphotropic virus
ICE	Immune Effector Cell-associated Encephalopathy
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IND	Investigational New Drug
INDSR	Investigational New Drug Safety Report
IO	Insertional oncogenesis
irRC	Immune-related Response Criteria
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
LAGE-1a	L antigen family member-1a
LFT	Liver function test
LTFU	Long-term follow-up
MedDRA	Medical Dictionary of Regulatory Activities
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association

OS	Overall survival
ORR	Overall response rate
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RAP	Reporting and Analysis Plan
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Stable Disease
SIN	Self-inactivating
SPM	Study Procedures Manual
SUSAR	Suspected unexpected serious adverse reactions
TCR	T cell receptor
TGF	Tumor growth factor
TIL	Tumor-infiltrating lymphocyte
TLC	Tranfer factor of the lung for corbon monoxide
TNF	Tumor necrosis factor
ULN	Upper limits of normal
US	Ultrasound
VSV-G	Vesicular stomatitis virus G protein
WBC	White blood cell
WOCBP	Woman of child-bearing potential

APPENDIX 2. ECOG PERFORMANCE STATUS

Grade	ECOG
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

Source: (Oken, 1982)

APPENDIX 3. LOCAL LABORATORY TESTS AND ECG PARAMETERS

Clinical Chemistry:	Calcium Phosphorus Magnesium Albumin Bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Lactic acid dehydrogenase Sodium Potassium Bicarbonate Creatinine* Chloride Glucose Urea * In subjects <65 years of age creatinine clearance will be calculated using the Cockcroft-Gault Method: *Subjects ≥65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement, according to standard practice at the treating institution.
Coagulation Screen:	Prothrombin time *or* International Normalized Ratio Activated partial tissue thromboplastin time
ECG Parameters:	Heart Rate Heart Rhythm PR Interval RR Interval QRS Interval QTc Interval (Fridericia's or Bazett's correction)
Hematology:	Red cell count Hemoglobin Hematocrit Mean cell volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelet count White blood cell count & differential count (percent & absolute)
Lymphocyte subset	Absolute cell count and percentage of CD3, CD4, and CD8

Pregnancy Test:	Serum beta-HCG or Urine test
Thyroid Function Tests:	TSH with reflex free T4
Urinalysis:	Glucose Ketones Specific gravity Protein Blood Microscopy Bilirubin pH
Infectious disease markers:	HIV 1+2 antibody Hepatitis B core antibody – if positive, test for HBV DNA Hepatitis C antibody – if positive, test for HCV RNA HTLV 1+2 IgG CMV IgG / DNA PCR Epstein-Barr virus (EBV) (EBNA) Syphilis (spirochaete bacterium) rapid plasma regain
Other Tests:	Uric Acid C-reactive protein

APPENDIX 4. RECIST 1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS

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

Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

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

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

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

Measurable lesions

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

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

Measurable lesions

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

- **'Cystic lesions'** thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Non-measurable lesions

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

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

Target Lesions

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

Non-target Lesions

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

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is

the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions) Note: determination of PD will not be made prior to the Week 8 evaluation.

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

Evaluation of Non-Target Lesions

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

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

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

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

Special notes on the assessment of target lesions

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

Special notes on the assessment of non-target lesions

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

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

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

New lesions

The appearance of new malignant lesions denotes disease progression:

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

It is sometimes reasonable to incorporate the use of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

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

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

**Only for non-randomized trials with response as primary endpoint.

***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

Confirmation

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

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

Missing Assessments and Inevaluable Designation

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

argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

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

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

Table 15 : Schedule of Procedures for Second T Cell Infusion (Interventional Phase 2)

	Baseline[1]		Interventional Phase 2																		Completion/ Withdrawal[5]
			Lymphodepleting Chemotherapy[2]			T-cell in-fusion[3]	Post-T-cell Infusion														
Day (D) / Week (W)	**-28 D[4] of Chemo-therapy**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafte r**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**			**±7 days**				**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	14	17	19	20	21	22	23-28	29+	
	Clinical Assessments and Procedures[6] (refer to Section 7.4 for details)																				
Informed Consent[7]	X																				
Inclusion/ Exclusion	X[8]																				
Medical History[9]	X																				
Physical Exam	X					X					X	X									
Prior/Concomi-tant Medications[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X					X					X	X	X	X	X	X		X	X	X	X
Vital Signs / Height/ Weight[11]	X					X[12]	X	X	X	X	X	X									X
ECG	X					X			X		X										

	Baseline[1]		Interventional Phase 2																		Completion/ Withdrawal[5]
			Lymphodepleting Chemotherapy[2]			T-cell infusion[3]	Post-T-cell Infusion														
Day (D) / Week (W)	**-28 D[4] of Chemotherapy**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafte r**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**			**±7 days**				**±14 days**	**±3 mos**	**n/a**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**	**17**	**19**	**20**	**21**	**22**	**23-28**	**29+**	
ECHO/MUGA	X																				
CT / MRI [13]	X													X		X		X	X	X	X
Brain MRI	X		See footnote 27																		
ICE[29]						See footnote 28															
Chest X-ray	X																				
PFTs[14]	X																				
Lymphocyte subset (CD3/CD4/CD8)	X																				
Hematology	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Coagulation Tests	X[4]																				
Pregnancy Test[15]	X	X				X							X	X	X	X	X	X	X	X	X
Urinalysis	X[4]																				
Infectious disease markers[16]	X																				

	Baseline[1]		Interventional Phase 2																		Completion/ Withdrawal[5]
			Lymphodepleting Chemotherapy[2]			T-cell in-fusion[3]	Post-T-cell Infusion														
Day (D) / Week (W)	**-28 D[4] of Chemo-therapy**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**			**±7 days**				**±14 days**	**±3 mos**	**n/a**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**	**17**	**19**	**20**	**21**	**22**	**23-28**	**29+**	
CMV IgG and PCR[17]	X					X						X	X	X						X	
TSH with free T4[18]	X																				
CRP[19]	X					X			X		X	X	X								
Uric acid	X					X															
GFR or 24h urine[20]	X																				
Adverse Events[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vector Copies (Persistence for Safety)[22]						X											X	X[22]	X[22]		
VSV-G DNA (RCL)[23]						X									X			X	X[23]	X[23]	
ICE[24]	**See footnote 24**																				
	Lymphodepleting Chemotherapy[2] & Investigational Product Administration																				

	Baseline[1]		Interventional Phase 2																		Completion/ Withdrawal[5]
			Lymphodepleting Chemotherapy[2]			T-cell in-fusion[3]	Post-T-cell Infusion														
Day (D) / Week (W)	**-28 D[4] of Chemo-therapy**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Therea fter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**			**±7 days**				**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	14	17	19	20	21	22	23-28	29+	
Fludarabine		X	X	X	X																
Cyclophos - phamide			X	X	X																
NY-ESO-1[c259]T						X															
	Correlative Studies and Research Assessments (refer to Section 7.5 for details)																				
Tumor biopsy[25]	X[25a]													X							X
Liquid biopsy[25]	X					X					X		X	X		X					X
Cell phenotype and Functional Assays,						X			X		X	X	X	X	X						X
Cytokine Analyses[19] & Humoral Anti- Infused Cell Responses						X[26]	X	X	X	X	X	X	X	X[26]	X						

	Baseline[1]		Interventional Phase 2																	Completion/ Withdrawal[5]
			Lymphodepleting Chemotherapy[2]			T-cell infusion[3]	Post-T-cell Infusion													
Day (D) / Week (W)	**-28 D[4] of Chemotherapy**	**D -8**	**D -7**	**D -6**	**D -5**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**Every 3 Mos Until Yr 2.**	**Every 6 Mos Thereafter**	
Visit Window		**n/a**	**n/a**	**n/a**	**n/a**	**n/a**	**±1 day**					**±3 days**				**±7 days**			**±14 days**	**±3 mos**	**n/a**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	14	17	19	20	21	22	23-28	29+	
Vector Copies (Persistence) for Research	X[1]					X	X		X		X	X	X	X	X	X					X

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

1. Subjects must have been considered eligible for a second infusion (refer to Section 4.4) before initiating any screening procedures or assessments for Interventional Phase 2.
2. Refer to Section 5.2 for details on prophylaxis therapies, pre-medications, fludarabine dose adjustments according to renal function, and supportive treatments.
3. All samples will be collected and assessments performed prior to T-cell infusion, unless otherwise specified.
4. Clinical procedures or assessments do not need to be repeated at this Baseline visit if they were be performed within 28 days of planned leukapheresis, with the exception of lymphocyte subset (CD3/CD4/CD8), hematology, chemistry, coagulation and urinalysis which must be done within 7 days of leukapheresis.
5. If a subject withdraws consent or completes the Interventional Phase 2, all procedures and assessments listed at this visit must be performed, unless done within the previous 30 days.
6. All clinical assessments and procedures must be performed as indicated; however, any clinical assessment or procedure can be performed if clinically indicated at any time.
7. An additional written subject informed consent for a second infusion must be obtained prior to performing any Baseline assessments or procedures, unless otherwise specified.
8. Subjects must continue to meet all eligibility criteria (Section 4.2 and Section 4.3) in addition to meeting those prior to second infusion specified in Section 4.4).
9. Any new or changes in medical history will be recorded in the EDC at Baseline visit; however, any additional changes in medical history must be recorded in source documents throughout the conduct of the study.
10. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.
11. Includes temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. Height will be collected at the Screening visit only.

[12.] Vital signs on day of T cell infusion should be taken pre-infusion, and at 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
[13.] If a subject is found to have a tumor response or PD by imaging, a follow-up confirmation scan must be done no earlier than 4 weeks following the scan when response or PD first seen. A subject is not considered to have a response or PD until follow-up scan confirms the finding.
[14.] Includes FEV1, FVC, TLC, and DLCO parameters to determine eligibility as described in Exclusion criterion #10.
[15.] FPCP must have a negative urine or serum pregnancy test.
[16.] Includes HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochaete bacterium). Refer to Exclusion criterion #12 for details on required testing for eligibility.
[17.] Only subjects who are CMV IgG seropositive at baseline will continue to be monitored for CMV viremia by CMV DNA PCR post baseline.
[18.] A free T4 test should be performed in subjects who have an abnormal TSH function test (high or low).
[19.] If CRS is suspected, cytokine and C-reactive protein levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.
[20.] Only to be done in subjects ≥65 years of age to measure renal function.
[21.] Adverse events should be reported as noted in Section 9.
[22.] Persistence of gene modified cells in subjects will be monitored at Months 3, 6, and 12 post-infusion, then every 6 months until 5 years post-infusion and annually from year 6-15 post infusion. If no gene modified cells are detected for 3 consecutive assessments post-infusion, and subject is >5 years post-infusion, then sample collection may stop.
[23.] If RCL tests are negative at all time points during the first year, then samples will be collected annually and archived for up to 15 years post or until assessments for persistence have ended However, if VSV-G DNA copies are detected at any time point in the first year post-infusion, refer to the safety monitoring proceduresin Section 10.5.
[24.] Immune Effector Cell-Associated Encephalopathy (ICE) should be measured on the day of NY-ESO-1c259T cell infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. Subjects with know brain metastases should be monitored at least twice per day for the first 5 days following NY-ESO-1c259T cell infusion. If a subject is found to have Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), the ICE neurological assessment tool, should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated .
[25.] Core needle biopsies are at baseline, week 8, and at confirmation of PD, with the exception of subjects for whom there is no safely accessible tumor tissue. 24a.) If a fresh biopsy was taken to confirm continued expression of NY-ESO-1 and/or LAGE-1a at the time of PD after the first T cell infusion and there is sufficient tumor sample left remaining, this sample may be used as the baseline sample. Otherwise, the baseline biopsy should be collected anytime two weeks prior to the start of lymphodepleting chemotherapy, with preference closer to the time of infusion. 24b.) Exosome/cfDNA samples should match tumor biopsy time points.
[26.] Pre-infusion and Week 8 blood collection is for both Cytokine and Humoral anti-infused cell responses, and is collected in one 3 ml tube.
[27.] Brain MRI will be performed at baseline for all participants and as clinically indicated thereafter (see Section 8.9.2).

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APPENDIX 7. PROTOCOL CHANGES

Amendment 01 Changes

The original Protocol dated, 08 June 2015, was replaced by Amendment No. 01, Protocol, dated 08 August 2016. This amendment applied to all participating investigative sites.

The following protocol changes were implemented by Adaptimmune as a result of emerging data from Adaptimmune's clinical development program as well as comments received by the participating investigative sites and Regulatory Authorities.

Additionally, protocol changes were made to align with Adaptimmune's standard protocol language. Due to these revisions, the section numbering changed. The previous section number has been noted in the table below.

Table 16 Summary of and Rationale for Protocol Changes

Section of Protocol	Changes	Rationale for Changes
Title and Clinical Study Protocol pages	Changed from Phase I/II to Pilot Added Eudra Number	To better reflect the aim of the trial which is to test a drug or treatment in a small group of people in a new indication (NSCLC) for the first time to evaluate its safety and identify side effects. To reflect study participation in EU countries
Investigator Signature and Sponsor Signature/ Information Pages (previously Section 16 in original protocol)	Moved to two separate pages after the title page	To adhere to Adaptimmune's recently developed standard protocol template
Synopsis	Revised to reflect changes made throughout protocol as described herein	To ensure consistency with protocol following amendment
Section 1 Background and Study Rationale (previously Section 2 in original protocol)		
Section 1.2: Background to Adoptive T Cell Therapy (previously Section 2.1 in original protocol)	Text was deleted and reference to NY-ESO-1^{c259}T Investigator Brochure added	To minimize information provided in the MAGE-A10^{c796}T Investigator Brochure.
Section 2.3 through Section 2.7 in original protocol	Sections deleted	To minimize information provided in the MAGE-A10^{c796}T Investigator Brochure.
Section 1.3: Adoptive Immunotherapy with NY-ESO-1 Specific T Cells and Supporting Data in NSCLC and Section 1.4 Rationale for NY-ESO-1^{c259}T for NSCLC (previously Section 2.8 in original protocol)	Section headings split (from 2.8 to 1.3 and 1.4) Added expression rates for LAGE-1a in NSCLC	To adhere to Adaptimmune's recently developed standard protocol template LAGE-1a and NY-ESO-1 share the same peptide sequence that is displayed in HLA*02:01 on the surface of tumor cells; therefore, subjects will be screened for LAGE-1a in addition to NY-ESO-1 in the Screening Protocol (ADP-0000-001) to determine eligibility for this study. To provide information on LAGE1a in this this patient population, the expression rates in various histology was added.

Section 1.4.1: Optimization of Lymphodepleting Chemotherapy Regimen (not previously part of original protocol)	Section added to provide rationale for change in lymphodepleting chemotherapy regimen	Based on emerging data from CAR-T cell clinical studies and Adaptimmune's ongoing clinical program, the lymphodepleting chemotherapy regimen was changed from cyclophosphamide alone to cyclophosphamide plus fludarabine. Data indicates that the addition of fludarabine to cyclophosphamide may play a role in homeostatic expansion.
Section 2: Trial Objectives and Endpoints (previously Section 3 in original protocol)		
Primary endpoint	Added anti-NY-ESO-1^{c259}T antibodies, persistence, and circulating cytokines as safety endpoints	To better characterize the comprehensive safety evaluation to be performed for this study. Previously these were listed as separate secondary objectives of the study.
Secondary objective: To evaluate the efficacy of NY-ESO-1^{c259}T	Removed text defining secondary efficacy endpoints; Deleted clinical benefit rate and added overall best response as secondary efficacy endpoint	Text was removed to minimize information provided in the Statistical Analysis Plan and Section 11.5 of the protocol To more clearly define an evaluation of tumor response by using the standard overall best response as assessed by RECIST 1.1.
Secondary and Exploratory objectives/endpoints	Revised text around correlative science objectives and re-classified them as exploratory objectives	To better characterize the correlative studies and research assessments to be performed in this study. To properly denote objectives as exploratory and to ensure alignment with Adaptimmune's recently developed standard protocol template.
Section 3: Investigational Plan (previously Section 4 in original protocol)		
Section 3.1 Overall Study Design (previously Section 4 and Section 4.2 in original protocol)	Added text providing guidance on patient management in terms of hospitalization Removed language around HLA and antigen testing as screening tests for this study and added text to denote that HLA and antigen testing will have been conducted in the Screening Protocol (ADP-0000-001).	To ensure the safety of subjects, language was added noting that hospitalization for lymphodepleting chemotherapy is at the discretion of the Investigator; however, inpatient hospitalization was recommended for T cell infusion to allow for close monitoring. To ensure subjects will have completed testing for HLA subtype and antigen expression in the context of the Screening Protocol and that HLA and antigen expression satisfies the requirements of this protocol before undergoing written informed consent and screening procedures associated with this study. Additional revisions to language was made to adhere to Adaptimmune's recently developed standard protocol template.

Section 3.2.1: Screening for HLA and NY-ESO-1 (ADP-0000-001) (previously Section 2.9 in original protocol)	Revised language in accordance with protocol template	To adhere to Adaptimmune's recently developed standard protocol template.
Section 3.2.2: T Cell Manufacturing (previously Section 2.6 in original protocol)	Revised text to concisely and at a high-level describe the T cell manufacturing process Text was revised around the timing of when manufactured T cells would be shipped to the sites	To minimize information provided in the NY-ESO-1^{c259}T Investigator Brochure and to adhere to Adaptimmune's recently developed standard protocol template. To acknowledge that the manufacturer will now ship the T cell product after the 14-day (not 7-day) sterility testing is complete and the release specification acceptance criterion is confirmed to have been met. Therefore, T cells will arrive approximately 28 days after leukapheresis instead of 21-28 days. Furthermore, to accommodate ex-US sites which may not have sufficient storage facility for the T cell product, shipment will occur immediately before the scheduled infusion and may be stored in the cryoshipper.
Section 3.2.3: Lymphodepletion (previously Section 4.1.1. in original protocol)	Revised text to provide rationale for change in lymphodepleting chemotherapy regimen	Based on emerging data from CAR-T cell clinical studies and Adaptimmune's ongoing clinical program, the lymphodepleting chemotherapy regimen was changed from cyclophosphamide alone to cyclophosphamide plus fludarabine. Data indicates that the addition of fludarabine to cyclophosphamide may play a role in homeostatic expansion.
Section 3.2.4.: T Cell Infusion (previously Section 6.2 in original protocol)	Moved section to be part of Rationale for Components of Study Design	To adhere to Adaptimmune's recently developed standard protocol template.
Section 3.2.5.: Rationale for NY-ESO-1^{c259}T Cell Dose (previously Section 4.1.2. in original protocol)	Updated text to include cell dose ranges from current NY-ESO-1^{c259}T cell ongoing studies	To provide current information from our ongoing clinical program which continue to provide support for the cell dose ranges being explored in this study.
Section 4.1.3 and Section 4.1.4 in original protocol	Sections deleted	To remove repetitive language around tumor assessment criteria (RECIST v1.1) and Correlative studies which is covered elsewhere in the protocol
Section 3.3.: Number of Subjects and Duration of Study (previouslySection 4.4 in original protocol)	Added estimation of study enrolment and study completion	To provide context around the duration of the study in terms of enrolment and completion

Section 3.4 Sites (previously Section 4.5 in original protocol)	Increased number of sites 15 and noted region as North America and Europe	To reflect an increase in the number of sites globally needed to recruit this patient population
Section 3.5: Benefit: Risk Assessment (not previously part of original protocol)	Section added	Based on pre-clinical and clinical studies of NY-ESO-1^{c259}T, this section provides the potential benefits and risks of NY-ESO-1^{c259}T and the mitigation strategy for this study
Section 4.: Selection of Study Population, Withdrawal, Completion and Stopping Criteria (previously Section 5 in original protocol)		
Section 4.1 Overview (previously Section 5.1 in original protocol	Deleted text	To remove repetitive language (patient population and participation in pharmacogenetics research) previously presented in other sections of the protocol
Section 4.2.1. Inclusion criteria (previously Section 5.2.1 in original protocol)	Added text around ROS1 gene rearrangements in inclusion criterion #5 (previously #3). Added the following criterion: #12. "Subject is fit for leukapheresis and has adequate venous access for the cell collection" Revised text around effective birth control in inclusion criterion #13 (previously #9) Revised laboratory values defining adequate organ function for eligibility in inclusion criterion #14 (previously #10)	Given the additional indication of crizotinib for patients with metastatic NSCLC whose tumor are ROS1 positive, text was added to clarify that such subjects should have received this standard of care treatment when appropriate. To ensure the safety of subjects by selecting those who can undergo the process of leukapheresis, including the appropriate venous access to obtain the required cells for manufacturing. To ensure female subjects are using the appropriate birth control for a defined time period after cell infusion (12 months) or after there is no evidence of persistence/gene modified cells in the blood (4 months). To ensure male subjects are using the appropriate birth control for a defined time period after chemotherapy according to the current available label. Also added a definition for abstinence for clarity of this means of birth control. To more accurately reflect the baseline status of subjects with advanced NSCLC, certain laboratory values which define adequate organ function have been revised. Acceptable baseline values for ANC, hemoglobin, and platelets were lowered; however, remain in a safe range (i.e., subjects are not at risk for infection or spontaneous bleeding). A required white blood cell count was removed because a minimum WBC is not needed to determine eligibility if a

		minimum ANC is specified. Creatinine clearance rate has been lowered from ≥50 mL/min to ≥40 mL/min to be in line with the fludarabine administration guidelines. Alkaline phosphate was removed from the eligibility criteria because it is a non-specific test that can be out of normal range for a variety of reasons, including due to advanced malignancy, and does not impact ability to tolerate T cell therapy.
Section 4.2.2. Exclusion criteria (previously Section 5.2.2. in original protocol)	Revised wash-out interval for immune therapy from 3 weeks to 4 weeks prior to leukapheresis in exclusion criterion #1 Revised exclusion criterion #2 to allow subjects with stable or irreversible Grade 2 toxicities to be enrolled on a case-by-case basis with prior consultation and agreement with the Sponsor Study Physician. Revised exclusion criterion #3 to include fludarabine. Removed bullet from exclusion criterion #10: "Clinically significant psychiatric illness/social situations that would limit compliance with study requirement" and replaced with wording "Subjects who in the opinion of the Investigator will be unlikely to fully comply with protocol requirements" Revised text around exclusion criterion #11 regarding active infections, including the addition of HTLV 1 and 2 testing	The average half-life of most monoclonal antibodies is 3 to 4 weeks; therefore, to allow for a sufficient wash-out for monoclonal antibodies that have longer half-lives, this interval was increased To enable subjects with stable pre-existing toxicity the opportunity to enroll onto the study following the appropriate consultation To ensure safety of subjects by excluding those who have a history of allergic reactions to fludarabine which has been added to the lymphodepleting chemotherapy regimen To broaden the scope of excluding those subjects who will be most likely be noncompliant according to Investigator's assessment To provide clarity on the serology testing required to rule active hepatitis B and C infection. FDA guidance states that whole blood and blood components intended for use in transfusion and leukocytes intended for manufacturing use should be screened for antibodies to HTLV-I. Only units from donors found to

		be negative on screening test(s) for antibodies to both HTLV-I should be released for use in transfusion; therefore screening for HTLV was added.
Section 4.3 Additional Eligibility Criteria (Prior to Lymphodepleting Chemotherapy) (previously Section 5.3 in original protocol)	Added text to allow prior treatment with PD-1 and PD-LI inhibitors in inclusion criterion #1	Given the recent approval and availability of treatment with PD-1 and PD-L1 inhibitors, text was added to clarify that prior treatment with such therapy was allowed
Section 4.4. Additional Eligibility Criteria (Prior to Second T-Cell Infusion) (not previously part of original protocol)	Added eligibility criteria for subjects to meet prior to second T cell infusion	To ensure consistency across our clinical studies in NSCLC, inclusion and exclusion criteria were added to this protocol allowing for a rigorous evaluation of eligibility before a subject receives a second infusion.
Section 4.5. Completion of the Interventional Phases and Section 4.6: Subject Withdrawal (previously Section 7.3 in original protocol)	Revised text around subject completion to also include subjects who died prior to disease progression	To clarify that subjects who have disease progression or die prior to disease progression are considered to have completed the study
Section 4.7: Consideration for Temporary Suspension of Enrollment (previously Section 11.1 in original protocol)	Revised text around stopping rules by changing two or more Grade 4 events to two or more Grade 4 <u>autoimmune</u> events and added text for an additional criteria around positive RCL	To clarify that the clinically significant events must be autoimmune in nature and a confirmed positive RCL can be either through positive PBMCs or biological to trigger a temporary pause in enrolment to allow for a comprehensive assessment by Adaptimmune's Safety Governance Board. Additional revisions to language was made to adhere to Adaptimmune's recently developed standard protocol template.
Section 5: Study Treatments (previously Section 6 in original protocol)		

Section 5.1.: Leukapheresis (not previously part of original protocol)	Section added	To provide instructional language on how to obtain starting material for the manufacture of autologous NY-ESO-1^{c259}T.
Section 5.2: Lymphodepleting Chemotherapy (previously Section 6.1 in original protocol)	Revised text to provide information on the administration of cyclophosphamide and fludarabine Added sections to provide information on recommended prophylaxis and supportive medication, including Mesna	To provide comprehensive information on how to administer cyclophosphamide and fludarabine in terms of days, route and dosage, including dose adjustment of fludarabine according to renal function. To provide detailed information on prophylactic treatment for infection, pre-medication, including hydration and anti-emetics, administration of Mesna and G-CSF.
Section 5.3: T Cell Infusion (previously Section 6.2 in original protocol)	Revised text to provide information on the infusion of the T cell product	To provide comprehensive information on how to infuse the NY-ESO-1^{c259}T cell product, including pre-medication, thawing and transport instructions, use of dual spike infusion set, and handling of adverse reactions.
Section 5.4: Second T Cell Infusion (previously Section 6.3 in original protocol)	Revised text to provide information around a second T cell infusion, now defined as Interventional Phase 2	To provide comprehensive information on the eligibility requirements for a second T cell infusion as well as the assessments required in-between infusions and at the time of Screening for Interventional Phase 2 (second T cell infusion)
Section 6: Concomitant Medication and Treatment (previously Section 7 in original protocol)		
Section 6.1: Prohibited concomitant medication and treatment (previously Section 7.1 in original protocol)	Deleted text Corrected text regarding the administration of steroids as anti-emetics	To remove repetitive language (prohibited anti-cancer treatments and required wash-out intervals) previously presented in other sections of the protocol. To clarify that steroid administration is started before (not after) chemotherapy in accordance with ASCO guidelines
Section 6.2.: Permitted Concomitant Medication and Treatment (previously Section 7.2 in original protocol)	Added text on the use of vaccines Added text defining concomitant medications	To provide guidance on the immunization of a high-risk subject (or member of the subject's household) To provide instructions on the data collection requirements for concomitant medications regarding type and the timeframe of interest
Section 7.3 in original protocol	Moved section regarding completion of and withdrawal from the study to Section 4.5 and Section 4.6, respectively	To adhere to Adaptimmune's recently developed standard protocol template

Section 7: Schedule of Assessments and Procedures (previously Section 8 in original protocol)		
Section 7: Schedule of Assessments and Procedures (previously Section 8.1, including 8.1.1 and 8.1.2 in original protocol)	Deleted text regarding screening number and subject identification number	To remove repetitive language (subject eligibility) previously presented in other sections of the protocol To provide clarification that subjects are assigned one unique 5-digit subject identification number that is assigned at the Screening Protocol and will serve as the same Subject ID for this study; this is a new process for Adaptimmune
Section 7.1.:HLA and Antigen Screening (to be conducted in Screening Protocol, ADP-0000-001) (previously Section 8.1 in original protocol)	Revised text to denote that HLA subtype and antigen expression screening is required in the Screening Protocol (ADP-0000-001)	To ensure subjects will have completed testing for HLA subtype and antigen expression in the context of the Screening Protocol and that HLA and antigen expression satisfies the requirements of this protocol before undergoing written informed consent and screening procedures associated with this study.
7.2.: Schedule of Procedures, Table 5 (previously Section 4.2 in original protocol)	Added the following assessments to the Schedule of Procedures table: • Tobacco use as part of medical history • Chest x-ray • Pregnancy test • CMV IgG and PCR • GFR or 24hr urine • TSH and free TS4 Added the collection of liquid biopsies (exosomes and cfDNA) to table. Added local lymphocyte subset panel (CD3/CD4/CD8) to table Removed the following assessments from the Schedule of Procedures table: • HLA testing	To obtain adequate evaluations in this patient population to ensure eligibility and define a pre-infusion baseline value To provide an alternative safer approach to tumor biopsies as an additional way to address the correlative research objectives of the study To provide guidance on absolute lymphocyte count and CD3 subset prior to leukapheresis To remove assessments (HLA and antigen expression testing) that will no longer be performed as part of this study or no longer thought to be necessary for the evaluation of safety (ferritin and cardiac troponin)

	• Antigen expression testing • Ferritin • Cardiac troponin Added window intervals around visits where applicable Added visits at Week 5, Week 6, Week 10 and Week 20 to table. Changed frequency of post-infusion follow up visits and ensured assessments required for long-term follow up were accounted for in Schedule of Procedures (previously Section 4.3 in original protocol) and in accordance with FDA and EMA guidance.	To provide flexibility for procedures to be performed as required for each visit To allow for close monitoring of bone marrow suppression and related cytopenias following lymphodepletion and T cell infusion, additional visits for collection of blood for local hematology were added. To decrease the frequency of visits (every 3 months instead of every 2 months) for subjects who have not progressed 6 months after T cell infusion; thereby, aligning with standard of care
Section 7.4: Clinical Assessments and Procedures (previously Section 8.3 in original protocol)	Revised text throughout section regarding the safety and efficacy assessments to be performed on study Revised Section 7.4.7 Tumor Response Assessments to include irRECIST for exploratory purposes (previously Section 8.3.6 in original protocol) Deleted Section 8.3.6.1 (in original protocol) regarding immune-related response criteria (irRC)	To ensure alignment with the assessments and timing of assessments presented in the Schedule of Procedures, Table 4 and to adhere to Adaptimmune's recently developed standard protocol template To provide an opportunity for new lesions to be assessed by the Investigator using irRECIST criteria for exploratory purposes; tumor response for assessment of efficacy will be according to RECIST v1.1 Nishino and colleagues [Clin Cancer Res; 19(14); 3936–43)] concluded that using unidimensional measurements (as required with RECIST criteria) yielded highly concordant response assessment compared with bidimensional measurements (as required with irRC), with less measurement variability. Therefore, to simplify the collection of tumor measurements and subsequent

		Investigator assessment of tumor response, irRC was removed from this study; tumor response for assessment of efficacy will be according to RECIST v1.1
Section 7.5: Correlative Studies and Research Assessments (previously Section 8.4 in original protocol)	Revised text to provide details on the research on blood and biopsy samples	To provide more detailed information on the type of analyses to be performed and the objective of each analysis and to adhere to Adaptimmune's recently developed standard protocol template.
Section 7.5.1.: Pharmacogenetics Sample (previously Section 8.4.1 in original protocol)	Deleted text	To minimize information provided in the NY-ESO-1^{c259}T SPM and to adhere to Adaptimmune's recently developed standard protocol template.
Section 7.5.2.:Cytokine and Soluble Factors analysis (not in original protocol)	Section added	To provide detailed information on the analyses planned for cytokines, growth factors and soluble receptors.
Section 8.4.3: Screening Assay in original protocol	Section deleted	To remove information no longer relevant for this study since antigen expression testing will be performed in the Screening Protocol (ADP-0000-001)
Section 7.5.3. Tumor biopsies (previously Section 8.4.23 in original protocol)	Revised text around tumor tissue collection Added text on collection of pleural effusion or ascites fluid	To clarify that the biopsy required at screening will be obtained and tested in the Screening Protocol (ADP-0000-001) and to provide additional details on the time points for biopsies Pleural effusion/ascites samples can be a rich source of tumor cells, tumor infiltrating leukocytes and soluble factors; therefore, text was added to allow for the collection of such samples for translational research studies.
Section 7.5.6: Liquid Biopsy Collection and Analysis (not in original protocol)	Section added	To provide an alternative safer approach to tumor biopsies as an additional way to address the correlative research objectives of the study
Section 7.5.7: Request for Autopsy for Death Following Administration of Gene Transfer Agents	Corrected text regarding guidance for autopsy	To clarify that autopsy can be requested in accordance with FDA and EMA guidance which is no longer mentioned in NIH RAC guidelines

(previously Section 8.4.6 in original protocol)		
Section 8: Supportive Care Guidance (previously Section 9 in original protocol)		
Section 8: Supportive Care Guidance	Added text	To ensure the safety of subjects treated on this study, guidance was provided such that hospitalization is recommended for T cell infusion and treating staff should be experienced in the administration of hematopoietic stem cell transplant and/ or other cell and gene therapy
Section 8.2 Infection (not in original protocol)	Section added	To ensure the safety of subjects treated on this study, information on measures to treat and prevent infection was provided
Section 8.3: Hematologic and Blood Product Support (not in original protocol)	Section added	To ensure the safety of subjects treated on this study, information on the use of blood products while on study was provided
Section 8.4: Management of Autoimmunity (not in original protocol)	Section added	To ensure the safety of subjects treated on this study, information on autoimmune reactions was provided
Section 8.6: Management of Graft-versus-Host Disease (GVHD) (not in original protocol)	Section added	To ensure the safety of subjects treated on this study, information on the diagnosis, grading, and management of GVHD was provided.
Section 8.7: Management of Pancytopenia with Bone Marrow Failure / Aplastic Anemia (not in original protocol)	Section added	To ensure the safety of subjects treated on this study, information on the management of pancytopenia was provided.
Section 8.8.1. Management of Neutropenia (previously Section 9.3 in original protocol)	Revised text	To clarify that G-CSF should be administered 24 (not 24 to 72) hours after chemotherapy and to provide flexibility in management by allowing use of long-acting (pegylated) G-CSF.
Section 9.4 Management of Cytokine Release Syndrome (in original protocol)	Section deleted and moved to Section 8.5	To delete information previously provided in other sections of the protocol due to Adaptimmune's recently developed standard protocol template

Section 9: Recording Adverse Events (previously Section 9 in original protocol)		
Section 9.1: Time Period for Collecting AE and SAE Information (not in original protocol)	Section added	To provide guidance on the nature of AEs/SAEs to be recorded in the EDC over the course of the study (i.e., during screening phase, Interventional Phase and LTFU)
Section 9.2.2. Assessment of Causality (previously Section 10.2.2. in original protocol)	Added text to define the scales of causal relationship (possibly/probably/definitely)	To provide guidance to the Investigator when determining the causal relation between the AE/SAE and NY-ESO-1^{c259}T.
Section 9.3. Reporting Serious Adverse Events (previously Section 10.3 in original protocol)	Revised definition of SAE Corrected method of reporting an SAE	To ensure consistency of the definition of a SAE with the "Code of Federal Regulations Title 21 Section 312.32: IND Safety Reporting" To clarify that SAEs must be reported to Adaptimmune by completing the SAE eCRF form (not a paper SAE worksheet)
Section 9.6: Regulatory Reporting Requirements for SAEs (previously Section 10.3.1. in original protocol)	Previous section on Standards for Expedited Reporting (SUSARs) (Section 10.3.1.) has been replaced	To provide a concise overview of Sponsor obligations for reporting SAEs to regulatory authorities and to adhere to Adaptimmune's recently developed standard protocol template.
Section 10.3.2. Reporting Guidelines for Other Observations in original protocol	Section deleted	To delete information previously provided in other sections of the protocol or that are no longer relevant
Section 10.8: Hospitalization, Prolonged Hospitalization or Surgery	Section deleted	To delete information previously provided in other sections of the protocol
Section 9.9: Laboratory Test Abnormalities as Adverse Events (previously Section 10.9 in original protocol)	Revised definition regarding laboratory abnormalities to be reported as AEs	To clarify and simplify that only Grade ≥3 laboratory value should be reported as an AE and provide additional guidance on numerical lab values which reach Grade 4.

Section 10: Safety Monitoring (previously Section 11 in original protocol)		
Section 10.1: Monitoring and Management of Replication Competent Lentivirus (previously Section 11.2 in original protocol)	Revised text	To ensure compliance with FDA and EMA guidance on the monitoring and management of RCL and to adhere to Adaptimmune's recently developed standard protocol template.
Section 10.2: Persistence Testing and Monitoring for Insertional Oncogenesis (previously Section 11.3 in original protocol)	Revised text	To ensure compliance with FDA and EMA guidance on the monitoring and management of persistence and to adhere to Adaptimmune's recently developed standard protocol template.
Section 11: Statistical and Data Analysis (previously Section 12 in original protocol)		
Section 11.1: Study Populations (previously Section 12.3 in original protocol)	Revised definitions of populations	To clarify that the ITT population will be the primary population for safety and efficacy analyses (not just safety) and to remove the minimum target and per protocol patient populations which were thought to be not relevant for this small, Phase 1 study with the objective of defining safety of NY-ESO-1^{c259}T.
Section 11.2 : Sample Size Calculations (previously Section 12.1 in original protocol)	Revised text	To provide further justification on the sample size of the study
Section 11.3: Interim Analyses (not in original protocol)	Section added	To clarify that no formal interim analyses are planned for this study
Section 12: Clinical Supplies (previously Section 13 in original protocol)		
Section 12	Revised text	To adhere to Adaptimmune's recently developed standard protocol template regarding the Investigational Product, including packaging/labelling, storage/handling and accountability

Section 13: Data Handling and Record Keeping (previously Section 14.1, Section 15.4, and Section 15.2 in original protocol)		
Section 13	Revised and compiled sections	To adhere to Adaptimmune's recently developed standard protocol template regarding data management, including case report forms, source documents, and data retention
Section 14: Study Monitoring (previously Section 14.2 and Section 14.3 in original protocol)		
Section 14	Revised text and compiled sections	To adhere to Adaptimmune's recently developed standard protocol template regarding site monitoring and audits
Section 15: Regulatory and Ethical Considerations (previously Section 14.4, 14.5, 14.7, 14.8, 14.9, 14.10, and 14.12, in original protocol)		
Section 15	Revised text and compiled sections	To adhere to Adaptimmune's recently developed standard protocol template regarding regulatory and ethical considerations for the study
Section 16: Appendices (previously Section 17 in original protocol)		
Appendix 1 List of Abbreviations (previously Section 1 in original protocol)	Revised text	To align with abbreviations used throughout the revised protocol
Appendix 3: Local laboratory Tests and ECG Parameters (previously Section17.2 in original protocol)	Revised table	To align with all laboratory and ECG requirements of the revised protocol
Section 17.3: Total Blood Volumes Collection Table in original protocol	Section deleted	To remove information that will now be presented in the SPM
Section 17.4: Immune-related Response Criteria in original protocol	Section deleted	To remove information no longer applicable to the conduct of the study
Appendix 5: Schedule of Procedures for Second T cell infusion (not in original protocol)	Section added	To provide comprehensive schedule of procedures for those subjects deemed eligible for a second T cell infusion

Amendment 02 Changes

Primary reason for amendment

Protocol Amendment No. 01, dated 08 August 2016 is replaced by Protocol Amendment No. 02.

Subsequent to the licensing of Adaptimmune product NY-ESO by GSK, the purpose of this protocol amendment is to:

- Delete or replace references to Adaptimmune or its staff with that of GlaxoSmithKline (GSK) and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with GSK processes and procedures;
- Update language relating to serious adverse event (SAE) reporting and safety monitoring;
- Update of lymphodepletion regimen throughout.

Section of Amendment No. 2.0	**Change**
RESPONSIBLE SPONSOR STUDY PHYSICIAN/SPONSOR INFORMATION PAGE, and Responsible Study Physician/SAE Contact Information	Updated as applicable
Throughout the document	• GSK study numbers added to former Adaptimmune study numbers • Adaptimmune replaced by GSK / “the Sponsor” where appropriate • “Adaptimmune’s Safety Review Team and Safety Governance Board” replaced with “the Sponsor” where appropriate. • Statistical Analysis Plan (SAP) replaced by Reporting and Analysis Plan (RAP) • Update of lymphodepleting regimen
Objectives	Primary, secondary and exploratory objectives updated.
Section 3.1 Overall Study Design	Study design amended to update screening requirements, and definition of interventional phase completion, and to describe follow-up of subjects. Study design schematic updated.
Section 3.2.2 Lymphodepletion	Lymphodepleting regimen for the study updated.
Section 3.5.2 Risk Assessment	Information on known safety profile updated. Potentila risk of non-infection encephalopathy added.
Section 4.2.1 Inclusion Criteria	Contraceptive requirements updated.

Section of Amendment No. 2.0	Change
Section 4.2.2, Exclusion Criteria	Exclusion of subjects with active liver or biliary disease added, prior/concomitant medication exclusion criteria amended, exclusion of subjects with CNS metastases added, and QTc criteria and details of hepatitis B and C tests amended.
Section 4.5 Completion of the Interventional Phases	Definition of completion of interventional phases amended.
Section 4.6, Subject Withdrawal	Details of follow-up attempts amended, and information with regards to subjects who voluntarily discontinued added.
Section 4.7, Consideration for Temporary Suspension of Enrollment	Text amended to match standard GSK procedures.
Sections 4.8 Liver Safety: Required Actions and Follow-up Assessments	New section added on liver safety requirements
Section 5.2 Lymphodepleting Chemotherapy	Lymphodepleting chemotherapy regimen for the study updated.
Section 6.3 Contraception	New contraceptive requirements added.
Section 7.1 HLA and Antigen Screening	HLA and antigen screening requirement amended.
Schedule of Procedures	Updated to add Brain MRI and CARTOX
Section 7.4.6 Cardiac and Other Assessments	Brain MRI and CARTOX 10 added
Section 7.4.8 Long-Term Follow-up	Long-term follow-up requirements updated.
Section 8.9 Management of Encephalopathy Syndrome	New section added to describe management of encephalopathy syndrome
Section 9.1 Time Period for Collecting AE and SAE Information	Time period for AE and SAE monitoring and reporting updated.
Section 9.2.2 Assessment of causality	Wording amended to GSK standard
Section 9.3, Reporting of SAEs	Wording amended to GSK standard. Procedure for SAE reporting updated.
Section 9.4 Reporting Criteria During Long-Term Follow-up (Years 1 to 15)	Reporting criteria amended
Section 9.6 Regulatory Reporting for SAEs	Wording amended to GSK standard
Section 9.7 Cardiovascular and Death Events	New section added to describe details of reporting deaths and cardiovascular events

Section of Amendment No. 2.0	Change
Section 9.8 Pregnancy	Timing of reporting pregnancy to GSK by Investigator added.
Section 9.11 Timelines for safety reporting	New section detailing timelines for safety reporting added.
Section 11.5 Statistical Methods for Efficacy Endpoints	Description of key secondary analyses updated in line with updated objectives.
Appendix 1 List of abbreviations and definitions of terms	Updated abbreviation list
Appendix 5 – Schedule of Procedures for Second T Cell Infusion (Interventional Phase 2)	Brain MRI added

Amendment 03 Changes

Protocol Amendment No. 02 is replaced by Protocol Amendment No. 03.

Primary reason for amendment:

Changes made to the protocol were requested by the FDA as a result of safety events which included 2 reports of Guillain-Barré syndrome in subjects who have received chemotherapy and GSK3377794 during clinical trials.

Section of Amendment No. 3.0	Change
Synopsis Key Inclusion/Exclusion Criteria	Addition of 'Prior or active demyelinating disease as an exclusion criterion'.
3.5.2 Risk Assessment	Update to risk assessment to add additional risk of Guillain-Barré syndrome and other demyelinating neuropathies.
4.2.2 Exclusion Criteria (#10)	Addition of 'Prior or active demyelinating disease as an exclusion criterion'.
9.3 Reporting Serious Adverse Events (SAEs)	Addition of all cases of Guillain-Barré syndrome or acute demyelinating neuropathy as a reportable SAE within 24 hours.
10. 1 Safety Review Team	Addition of GSK SRT.

10.1.1. Mandated Study Pause Due to GBS	Addition of Mandated Study Pause due to GBS
10.4 Monitoring and management for Demyelinating Neuropathy and other Neurological events	Addition of Monitoring and Management for Demyelinating Neuropathy and other Neurological events