TITLE PAGE

Protocol Title: A Pilot Study of NY-ESO-1^{c259}T Cells in Subjects with Advanced Myxoid/ Round Cell Liposarcoma

Protocol Number: 208469 (ADP-0011-007) / Amendment 10

Compound Number or Name: GSK3377794 (NY-ESO-1^{c259}T, letestregene autoleucel, lete-cel)

Development Phase: Phase 1 / 2

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY

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Carsten Goessl, MD Vice President Clinical Development, Cell and Gene Therapies Oncology Research and Development GlaxoSmithKline	**Date**

The signed page is a separate document.

Medical Monitor Name and Contact Information: can be found in the Study Reference Manual

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Date of Original Protocol: 23 May 2016

Amendment	Version	Date	Reason for Change
1	02	03-OCT-2016	Change in scope to Phase I/II pilot study. See Section 16.6 for further details
2	03	24-JUL-2018	The following changes have been made: • Updates to time periods that must elapse between cessation of various therapies prior to leukapheresis and prior to initiation of lymphodepleting chemotherapy ("wash-out" periods) • Typographical errors have been corrected and timings of assessments have been clarified • Option to increase the sample size, as well as the option to change the lymphodepletion regimen based on emerging data • Administrative changes to align with GSK processes and procedures. • Language relating to serious adverse event (SAE) reporting and safety monitoring has been updated. See Section 16.7 for further details
3	04	17-OCT-2018	Changes made to the protocol were requested by 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.
4	5	18-JUN-2019	Clarification on definitions of enrolment and intent to treat population.
5	06	13-DEC-2019	The following updates have been made: • Addition/clarification of delayed AE definition • Revised guidelines for the management of CRS • Revised guidelines for the management of encephalopathy syndrome • Adjustment to lymphodepletion regimen for safety purposes See Section 16.10 for detailed list of changes details.
6	07	17-FEB-2021	The following changes have been made: • Update of primary endpoint to be ORR based upon investigator assessment rather than ORR based upon independent review resulting in consistency between interim and final analyses • Insertion of secondary endpoint of ORR as assessed by independent review See Section 16.11 for detailed list of changes
7	08	17-FEB-2021	The following changes have been made: Section 7.6 has been added describing the potential for retreatment for those subjects who have had a confirmed CR or PR or SD ≥3 months and have residual manufactured drug product for a second infusion.

Amendment	Version	Date	Reason for Change
8	09	18-MAY-2021	• Changes to protocol have been made in reference to Dear Investigator Letter dated 03 May 2021 and Protocol and ICF clarification memorandum dated 11 May 2021 regarding mitigations put in place on active studies of GSK3377794 (letetresgene autoleucel, lete-cel), following the recent SAEs of fatal neutropenia (1 event) and decreased vision (1 event) • See Section 16.13 for detailed list of changes
9	10	04-NOV-2021	• Changes to the protocol made in reference to Dear Investigator Letter dated 21 Oct 2021 and Protocol and ICF clarification memorandum dated 25 Oct 2021 regarding safety mitigations implemented on active studies of GSK3377794. • See Section 16.14 for detailed list of changes
10	11	17-DEC-2021	• Changes made to subject eligibility criteria to allow second infusion with lete-cel (GSK3377794) in patients who have received other anticancer therapy after progression post first lete-cel infusion. • See Section 16.15 for detailed list of changes

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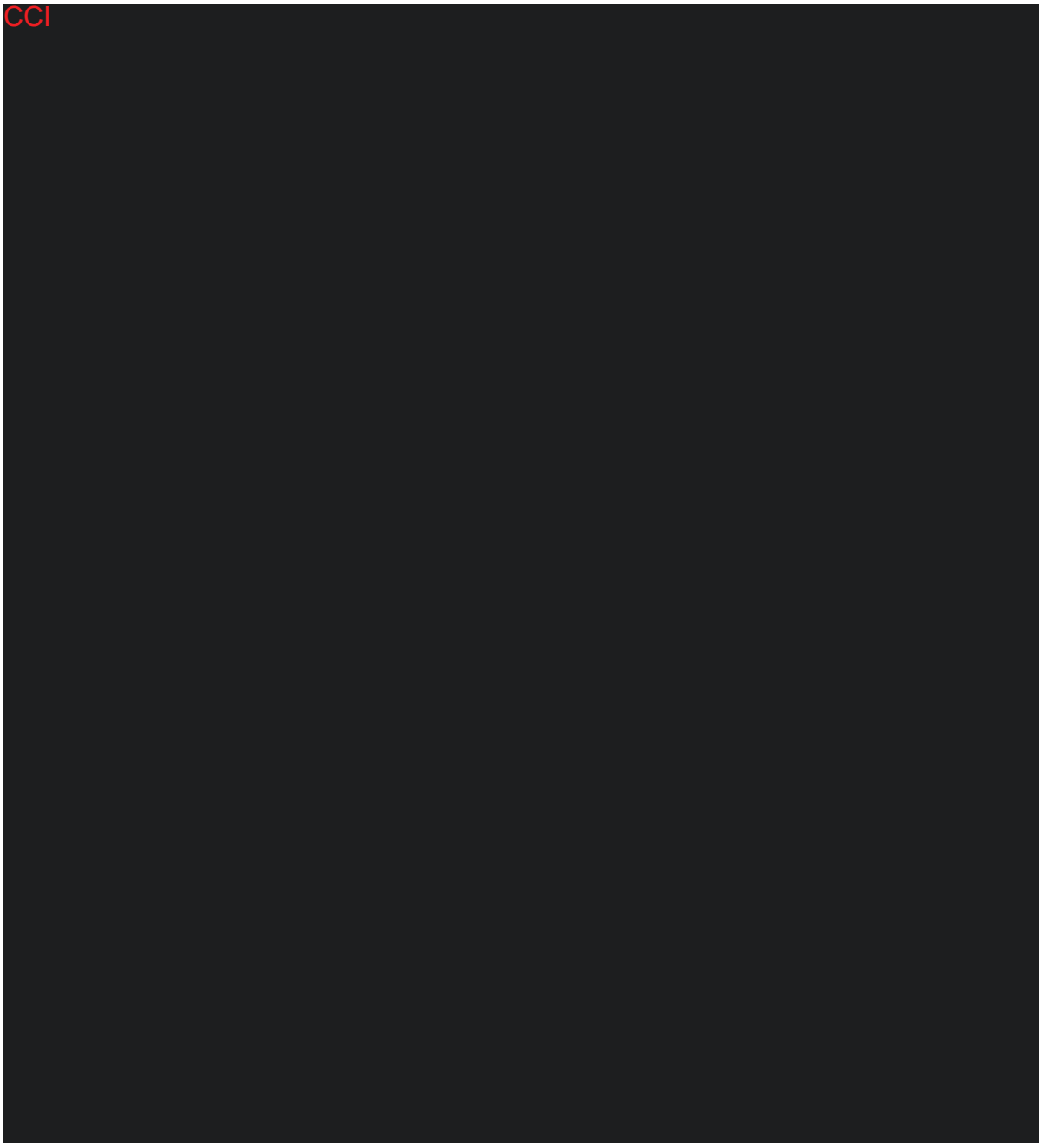
SYNOPSIS

Title	A Pilot Study of NY-ESO-1^{c259}T Cells in Subjects with Advanced Myxoid/ Round Cell Liposarcoma
Short Title	NY-ESO-1^{c259}T cells for Myxoid/ Round Cell Liposarcoma
Protocol Number	GSK208469 (ADP-0011-007)
Phase	I / II
Methodology	This is an open label pilot study of gene modified autologous T cells for the treatment of advanced myxoid/ round cell liposarcoma. 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 antigen above the cut-off level according to the applied immunohistochemistry, and who meet study entry criteria will be eligible for enrollment. Following enrollment, subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the NY-ESO-1^{c259} T cell investigational product. Once the NY-ESO-1^{c259}T cells have been manufactured subjects will receive lymphodepleting chemotherapy via two possible options. Option 1 (first 10 subjects) will involve lymphodepleting chemotherapy with fludarabine and cyclophosphamide on Days -7 to -5 and the study therapy by a single intravenous infusion on Day 1. Option 2 (second 10 subjects) will involve lymphodepleting chemotherapy with fludarabine on Days -8 to -5 and cyclophosphamide on Days -7 to -5 and the study therapy by a single intravenous infusion on Day 1. In Option 2, dose and regimen for lymphodepleting chemotherapy will be adjusted for subjects ≥60 years of age. There is no Day 0 in this protocol. Lymphodepletion may be given as outpatient treatment. The T cell infusion should be given as an inpatient procedure. Subjects may be hospitalized for follow-up care post T-cell infusion at the discretion of the investigator. Subjects will receive growth factor support with granulocyte colony stimulating factor (G-CSF) from 24 hours following lymphodepleting chemotherapy until neutrophil count recovery. Subjects will have the following study visits: Screening (visits 1 and 2), Leukapheresis, Baseline (Day -14 to Day -9), Lymphodepleting Chemotherapy (Day -8 or -7 to Day -5), NY-ESO-1^{c259}T cell infusion and immediate post infusion monitoring (Day 1 through Day 8), weekly until Week 6 post infusion, at 8, 10, 12, 16, 20 and 24 weeks, and then every 3 months until disease progression, death or until 2 years after NY-ESO-1^{c259}T cell infusion, whichever is shorter. Subjects will undergo disease monitoring by MRI or CT scan at screening, baseline, 4, 8, 12 and 24 weeks, and then every 3 months until progression of disease or until 2

	years after NY-ESO-1^{c259}T cell infusion, whichever is shorter. Investigators will assess tumor response according to RECIST v1.1 for clinical decision making and for determination of the primary endpoint. Scans will also be sent to a vendor for independent assessment of tumor response according to RECIST v1.1. Scans will be held until review requested by Sponsor. A tumor specimen (most recent archival or fresh biopsy) will be required to screen for NY-ESO-1 expression prior to leukapheresis. Tumor biopsies for research studies will be requested at Baseline (if a fresh biopsy was acquired at Screening another biopsy need not be taken at Baseline), Week 8 and upon disease progression with the exception for subjects with no safely accessible tumor tissue. Subjects who have received NY-ESO-1^{c259}T cell infusion will complete the interventional phase of the study upon disease progression, death or having been followed-up for 2 years after NY-ESO-1^{c259}T cell infusion, whichever is shorter. NY-ESO-1^{c259}T cell infused subjects who are alive on completing or withdrawing from the interventional phase will continue to be monitored in one of two ways: either via transfer to the Long Term Follow-Up (LTFU) protocol GSK208750 (ADP-0000-002) to monitor for gene therapy-related delayed adverse events for 15 years, in accordance with regulatory requirements for gene therapy clinical trials; or via continuance in the current trial until the LTFU protocol is available. If necessary, and upon discussion with the Sponsor, those patients who have not progressed after 2 years on study and who are continuing in Study 208469 may continue to undergo response assessments per institutional standard of care. Subjects who have achieved a confirmed CR or PR or SD lasting ≥3 months in response to their first NY-ESO-1^{c259}T cell infusion and have disease progression more than 3 months post infusion may be offered the option for retreatment if they have sufficient residual manufactured cells for a second T cell infusion. Retreatment involves all study procedures associated with the first infusion with the exception of leukapheresis and has exploratory efficacy and safety and tolerability objectives. Initially, 10 subjects will be treated/infused in this study. If further characterization of the treatment in this indication is required, a further 10 subjects may be treated/infused. The Sponsor may also decide to close the study at any time based on safety or efficacy.
Study Duration	Study enrollment is expected to continue for approximately 24 months. The study will be considered completed when the last subject has been rolled over into the LTFU protocol GSK208750 (ADP-0000-002), has completed long term follow-up in this study, has declined LTFU,

	has been withdrawn from this study (including lost to follow-up), or has died.
Study Center(s)	This is a multi-center study, including approximately 10 sites. Additional sites may be added at the discretion of the Sponsor.
Number of subjects	The target enrollment for this trial is up to 20 subjects treated, depending on emerging data. Up to 20 subjects may be treated/infused in total.
Objectives:	**Endpoints:**
Primary	
To evaluate the efficacy 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 subjects with NY-ESO-1 expressing advanced myxoid/ round cell liposarcoma	• Overall Response Rate[1] (ORR) per RECIST v1.1 by investigator assessment
Secondary	
To evaluate the efficacy 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 subjects with NY-ESO-1 expressing advanced myxoid/ round cell liposarcoma	• Overall Response Rate[1] (ORR) per RECIST v1.1 by independent review • Time to Response[2] • Duration of Response[2] • Progression Free Survival[2]
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 subjects with NY-ESO-1 expressing advanced myxoid/ round cell liposarcoma	• AEs, including SAEs and AESIs • Laboratory assessments, including chemistry and hematology • Replication competent lentivirus (RCL) • Instances of insertional oncogenesis • Incidence of anti-NY-ESO-1^{c259}T antibodies • ECG
To characterize the in vivo PK profile (levels, expansion, persistence) of NY-ESO-1 specific (^{c259}) cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit
Exploratory	
CCI [redacted]	

CCI



Subject Inclusion Criteria	A subject must meet the following inclusion criteria to be eligible for participation in this study: 1. Subject (or legally authorized representative) 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 at the time of signing the study informed consent 4. Subject has a diagnosis of high grade myxoid liposarcoma / myxoid round cell liposarcoma confirmed histologically and by the presence of the reciprocal chromosomal translocation t(12;16) (q13;p11) or t(12; 22) (q13;q12). 5. Subject has advanced (metastatic or inoperable) high grade myxoid liposarcoma / myxoid round cell liposarcoma. Inoperable refers to a tumor lesion in which clear margins cannot be obtained without leading to significant functional compromise 6. Subject has measurable disease according to RECIST v1.1 criteria. 7. Subject must be HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive. 8. Subject's tumor (either the most recent archival specimen or a fresh biopsy) shows positive NY-ESO-1 expression defined as ≥30% of cells that are 2+ or 3+ by immunohistochemistry. All samples must have been pathologically reviewed by a GSK designated central laboratory. 9. Subject must have previously received or be intolerant to anthracycline based therapy for advanced (metastatic or inoperable) disease. Subjects who received neoadjuvant/adjuvant anthracycline based therapy and progressed within 6 months of completion of therapy will be eligible. 10. Subject has an ECOG Performance Status 0-1. 11. Subject has a left ventricular ejection fraction ≥45%. 12. Subject is fit for apheresis 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. • 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 (WOCBP) 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: A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: • Is not a WOCBP as defined in Section 6.3.1 OR • Is a WOCBP (as defined in Section 6.3.1) 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 6.3.1 during the intervention period and for at least 12 months after receiving the T-cell infusion. In the event that there is evidence of persistence/gene-modified cells in the participant's blood, contraception usage should continue until 2 consecutive persistence tests show that GSK3377794 is below the level of detection in blood. 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.

14. Subject must have adequate organ function as indicated by the laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support)
Platelets	≥ 100 x10^9/L
Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to leukapheresis)
Coagulation	
Prothrombin Time or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Renal	
Calculated or measured creatinine clearance [1]	≥ 40 mL/min

1.

- Participants who are ≥18 and <65 years of age must be assessed either:
  - by 24-hour urine creatinine collection OR
  - by using Serum Creatinine (Scr) via an estimated creatinine clearance (CrCl) calculated as outlined below by using the Chronic kidney disease Epidemiology Collaboration (CKD-EPI) equation and adjusting the result by multiplying with (Body

Surface Area [BSA]/1.73) to obtain a CrCl in mL/min.

Step 1: estimated glomerular filtration rate (GFR) to be obtained from the CKD-EP) formula:

Estimated GFR (mL/min/1.73m^2) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 *[if female]* × 1.159 *[if black]*

where:

Scr is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
a is -0.329 for females and -0.411 for males,
min(Scr/κ,1) indicates the minimum of Scr/κ or 1,
max(Scr/κ,1) indicates the maximum of Scr/κ or 1, and
Age is in years.

Step 2: correction factor to be applied per the American National Kidney Foundation in order to obtain the estimated creatinine clearance in mL/min

Estimated CrCl (mL/min) = Estimated GFR (mL/min/1.73 m^2) × BSA (m^2) / 1.73

To calculate the BSA for fludarabine dosing, use actual body weight. An adjusted body weight may be required for cyclophosphamide.

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

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Subject Exclusion Criteria

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

1. Subject has received or plans to receive the following excluded therapy/treatment within the following periods prior to leukapheresis or lymphodepleting chemotherapy:

Treatment/Therapy	**Required Wash-out Prior to Leukapheresis**	**Required Wash-out Prior to Lymphodepletion**
Cytotoxic chemotherapy	3 weeks	3 weeks
Small Molecules/Tyrosine	1 week	1 week

	kinase inhibitor (TKI) such as pazopanib.		
	Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
	Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors, biologics)	2 weeks	2 weeks
	Experimental anti-cancer Vaccine	2 months in the absence of tumor response, or the subject should be excluded if their disease is responding to an experimental vaccine given within 6 months	2 months in the absence of tumor response, or the subject should be excluded if their disease is responding to an experimental vaccine given within 6 months
	Gene therapy using an integrating vector	Any use of previous gene therapy using an integrating vector is not permitted	Any use of previous gene therapy using an integrating vector is not permitted
	Allogeneic hematopoietic stem cell transplant (HSCT)	Any allogeneic HSCT is not permitted	Any allogeneic HSCT is not permitted
	Corticosteroids or any other immunosuppressive therapy. Use of topical steroids is not excluded.	2 weeks	2 weeks
	Investigational treatment	4 weeks	4 weeks
	Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician		
	2. Radiotherapy within the following periods prior to leukapheresis or lymphodepleting chemotherapy (Participant has received ≥50 Gy to a significant volume of the pelvis, long bones or spine, or a cumulative dose of radiation that, in the		

investigator's opinion would predispose patients to prolonged cytopenia after lymphodepletion):

Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Radiotherapy that involves the lung (V20 exceeding 30% lung volume) or pericardium (>20Gy). Exception for a lesser dose or radiation exposure to lung/mediastinum than stated, administered within 4 weeks prior to lymphodepletion. Electron beam radiotherapy to superficial structures in the chest is permitted.	N/A	3 months
Radiation to vital organs (e.g., liver, kidney)	N/A	4 weeks
Radiation to the pelvis	4 weeks	4 weeks
Whole Brain Radiotherapy (WBRT) or Brain Stereotactic Radiosurgery (SRS)	N/A	2 weeks
Radiotherapy to the target lesions	N/A	3 months prior to lymphodepleting chemotherapy. A lesion with unequivocal progression may be considered a target lesion. There is no washout period for palliative radiation to non-target organs.

3. Subject that has toxicity from previous anti-cancer therapy must have recovered to ≤ Grade 1 (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are

	deemed stable or irreversible (e.g., peripheral neuropathy) can be enrolled. 4. Subject has history of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study. 5. Subject has history of chronic or recurrent (within the last year prior to screening) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments. 6. Subject has known active brain or leptomeningeal metastases. Subjects with prior history of brain metastasis who have undergone local therapy (i.e., metastasectomy 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 prior malignancy that is not in complete remission. 8. Subject has electrocardiogram (ECG) showing clinically significant abnormality at Screening or an average QTc interval (Fridericia's or Bazett's formula) >450 msec in males and >470 msec in females (>480 msec for subjects with Bundle Branch Block (BBB)). 9. Subject has uncontrolled intercurrent illness including, but not limited to: – Ongoing or active infection, including but not limited to systemic fungal infection; EBV and CMV IgG seropositive patients who have a positive PCR – Prior or active demyelinating disease – Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4 – Uncontrolled clinically significant arrhythmia in last 6 months – Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months – Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent). 10. Subjects who in the opinion of the Investigator will be unlikely to fully comply with protocol requirements. 11. **ALT**>2.5 times ULN without documented liver metastases/tumor infiltration OR

	Total Bilirubin > 1.5 x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) 12. Subject has active infection with HIV, HBV, HCV or HTLV as defined below: – Positive serology for HIV – Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. – Active hepatitis C infection as demonstrated by test for hepatitis C RNA. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value – Positive serology for HTLV 1 or 2. Re-screening for infectious disease markers is not required at baseline (prior to lymphodepletion) 13. Subject is pregnant or breastfeeding.
Study Product, Dose, Route, Regimen	The investigational product (IP) in this study is autologous genetically modified NY-ESO-1^{c259}T cells (GSK3377794; letestregene autoleucel; lete-cel). The dose of NY-ESO-1^{c259}T will be within the range of 1 x 109 – 8 x 109 transduced cells. If the manufactured cell dose is less than the minimum dose of 1 x 109 transduced cells, 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. The cells will be administered by a single intravenous infusion on Day 1. Prior to administration of IP subjects treated under Option 1 will receive lymphodepleting chemotherapy consisting of fludarabine and cyclophosphamide on Days -7 to -5. Subsequently, subjects treated under Option 2 will receive lymphodepleting chemotherapy consisting of fludarabine on Days -8 to -5 and cyclophosphamide on Days -7 to -5.
Reference therapy	None
Statistical Methodology	After 10 evaluable subjects, response will be evaluated using Bayesian posterior predictive probabilities to inform clinical decision making to continue enrollment up to 20 evaluable subjects.

	The primary analysis population for safety will be the intention to treat population (ITT), where appropriate, defined as all subjects who underwent leukapheresis, and the modified intention to treat population (mITT), where appropriate, defined as all subjects who received NY-ESO-1^{c259}T cell infusion. The primary analysis population for efficacy will be the mITT population. The primary endpoint for efficacy is Overall Response Rate (ORR) defined as the proportion of subjects with a confirmed complete response (CR) or confirmed partial response (PR) via investigator assessment per RECIST v1.1 criteria relative to the total number of subjects in the analysis population. ORR will be summarized by two-sided 95% confidence intervals using exact and Wilson methods. 95% (Bayesian) credible intervals may also be used to summarize the ORR. Time to event endpoints will be summarized and displayed graphically using Kaplan-Meier (K-M) methodology to estimate the median, and the 25th and 75th percentiles if data warrant. Two-sided 95% confidence intervals will be produced. Overall Survival will be assessed at fixed time points such as 1 year and 2 years using K-M methods if data warrant. Descriptive statistics will be provided for disposition, demographic and safety data. All adverse events will be listed and coded by MedDRA. The number and percent of subjects reporting any adverse events will be tabulated by system organ class and preferred term. Adverse events will be further classified by toxicity (using CTCAE Version 4.0).

1. BACKGROUND AND STUDY RATIONALE

1.1. Adoptive T Cell Therapy

Adoptive T cell therapy (ACT) is a treatment that uses a cancer subject's own T lymphocytes with anti-tumor activity, expanded in vitro and re-infused into the subject. The ultimate objective of the process is the stimulation and expansion of potent and antigen-specific T cell immunity. There are numerous recent publications and reviews of adoptive T cell therapy [Kalos, 2013; Klebanoff, 2016; Maus, 2014; Morgan, 2010; 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 [Dudley, 2005; Besser, 2010]. 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 adoptive T cell therapy [Rapoport, 2005]. However, tumor cells are well known to be immunologically selected for low antigen presentation and the majority of tumor antigens are normally expressed self-antigens. Hence, the natural T cell receptors (TCRs) that recognize self- tumor antigens may be of low affinity. The high tolerance to tumor antigens with normal and/or developmental expression combined with the potent immunosuppressive microenvironment often present at the tumor site is manifest in most cases by suboptimal activation in terms of antitumor activity such that ‘‘native’’ T cells may not be sufficient to induce tumor cell death in most subjects with advanced malignancy. Higher affinity TCRs allow T cells to respond to lower levels of antigen; this is important for tumor immunotherapy where the tumor microenvironment has adapted itself to reduce expression of antigen and also decrease expression of MHC class I molecules [Marincola, 2000; Barrett, 2009].

Gene-transfer-based strategies have therefore been developed to overcome the consequences of immune tolerance on the tumor-specific T cell repertoire. These approaches provide the potential to redirect T cells to effectively target tumors by the transfer of antigen-specific affinity- optimized 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. 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 NY-ESO-1^{c259}T Investigator Brochure.

1.2. Adoptive Immunotherapy with NY-ESO-1 Specific T Cells and Supporting Data in Sarcoma

NY-ESO-1 is a member of the cancer-testis family of tumor antigens. An HLA-A2 binding peptide corresponding to amino acids 157 to 165 of NY-ESO-1 (SLLMWITQC) can be recognized by NY-ESO-1 reactive T cells and NY-ESO-1 epitopes are also recognized in the context of multiple HLA class II restriction elements. Several studies have demonstrated antibodies against NY-ESO-1 in patients with cancer. NY-ESO-1 may be particularly immunogenic.

T cells recognizing the immunodominant class I restricted HLA-A2 binding peptide have been used to clone a specific T cell receptor capable of recognizing this MHC restricted antigen. Further genetic engineering enhanced the affinity of this T cell receptor toward the SLLMWITQC peptide bound to HLA-A2. The result is an enhanced affinity T cell receptor designated as 1G4α95:LY TCR (c259 TCR), which shows pre-clinical activity in vitro and in vivo against NY-ESO-1 expressing HLA-A2+ tumors. The c259 TCR mediates efficient recognition by CD8+ T cells of the HLA-A2 bound peptide 157-165 and also mediates sufficient avidity to render CD4+ T cells capable of recognizing the 157-165 peptide in the context of HLA-A2. This co-receptor independent recognition implies high avidity of the 1G4α95:LY TCR, a potentially important property of clinically active T cell receptors. The enhanced TCR binds with similar affinity to HLA-A2 subtypes HLA-A*2:01, HLA-A*02:05, and HLA-A*02:06.

NY-ESO-1c259 SPEAR T cells (Specific Peptide Enhanced Affinity Receptor T cells) were initially investigated in collaboration with Surgery Branch of the National Cancer Institute (NCI) where the T cells were modified using a retroviral vector, expanded using NCI cell processing methods and administered in conjunction with IL2 following a lymphodepleting chemotherapy regimen consisting of cyclophosphamide (60 mg/kg/day for two days) and fludarabine (25 mg/m^2/day for five days). HLA-A2 subjects with NY-ESO-1 expressing (2-4+ intensity ≥ 50% of cells) synovial sarcoma (n=18) and melanoma (n=20) were enrolled in the study [Robbins, 2014]. Objective clinical responses were reported in 11 of 18 (61%) synovial sarcoma subjects with estimated overall 3- and 5- year survival rates of 38% and 14% respectively. Objective clinical responses were also reported in 11 of 20 subjects (55%) with melanoma, while the corresponding estimated 3- and 5- year survival rates for subjects with melanoma were both 33%.

The Adaptimmune/GSK sponsored clinical trial, “A Pilot Study of Genetically Engineered NY- ESO-1 Specific NY-ESO-1^{c259}T in HLA-A2+ Patients with Synovial Sarcoma” (ADP-04511; NCT01343043) was designed based on the NCI study, following publication of the preliminary study data [Robbins, 2008]. The current study differs from the original NCI study in that the T cells are transduced using a lentiviral vector, the product is manufactured using a proprietary cell processing technique in a central GMP

manufacturing site and the T cells are administered without the use of concomitant IL2. Confirmed responses (CR and PR) in Cohort 1 were observed in 6 of 15 subjects enrolled (40%), 6 of 12 (50%) subjects who received NY-ESO-1^{c259}T and 6 of 10 (60%) subjects who received at least a billion transduced cells. The median duration of response (DOR) was approximately 31 weeks with a range of 13 weeks-72 weeks (data cut-off of 31 August 2016). All subjects in this ongoing clinical trial, ADP-04511, are HLA-A2 (HLA-A2*02:01, HLA-A*02:05, and/or HLA-A*02:06) positive subjects with NY-ESO-1 expressing synovial sarcomas.

A recent immunohistochemistry study of NY-ESO-1 expression in tissue microarrays of 1132 intermediate and malignant mesenchymal tumors [Endo, 2015] confirmed strong expression (2 - 3+ in >50% tumor cells) in 49% of synovial sarcomas and also indicated expression in 88% of myxoid liposarcomas. This raises the possibility that myxoid liposarcomas may also be amenable to adoptive T cell therapy with NY-ESO-1^{c259}T cells.

1.3. Myxoid/Round Cell Liposarcoma

Sarcomas are rare malignant tumors originating from mesenchymal cells and their precursors, and represent ~1% of all cancers in adults worldwide each year (10% of cancers in children, and 8% of cancers in adolescents) and ~2% of cancer related mortality [Singer, 2000; Amankwah, 2013]. It is estimated that 11,930 new soft tissue sarcomas will be diagnosed (6,610 cases in males and 5,320 cases in females) in the United States in 2015, and approximately 4,870 Americans (2,600 males and 2,270 females) are expected to die of soft tissue sarcomas [Siegel, 2015]. Estimated incidence of soft tissue sarcoma in Europe averages 4 per 100,000 per year [Casali, 2009]. Soft tissue sarcomas (STS) consist of approximately 50 different histological subtypes.

Myxoid/ round cell liposarcoma (MRCLS) is a subtype of liposarcoma which is associated with specific translocations, t(12;16 (q13;p11) or t(12;22) (q13;q12) and represents about 30-35% of liposarcomas and 5-10% of all adult STS [WHO, 2002]. In the 2013 edition of the WHO classification, the term “round-cell liposarcoma” was removed as the prognosis and the frequency of metastasis in patients with myxoid liposarcoma is related to the degree of cellularity of the tumor rather than the presence of round cells vs spindle cells. In addition, the same molecular abnormalities are found in both round-cell and spindle-cell morphologies of high- grade myxoid liposarcoma [Doyle, 2014]. Therefore, patient diagnoses of “high grade myxoid liposarcoma” and “myxoid/ round cell liposarcoma” are equivalent when assessing patients for eligibility for this study, in accordance with the WHO 2013 classification [Fletcher, 2013].

MRCLS commonly presents at an age ranging from 35-55 years. The prognosis varies depending on the site of origin, the type of cancer cell, the tumor size, the depth and proximity to lymph nodes. MRCLS is prone to recur locally and, dependent on the histological grade, one-third of MRCLS cases will become metastatic with multifocal synchronous tumor spread to unusual bone and soft tissue locations and lung.

Myxoid tumor types have relatively favorable prognoses, with an ~80 -90% 5-year survival rate but tumors with a round-cell component >5% have a poor prognosis with a

5-year survival rate of ~50-75% because they recur locally and tend to metastasize quickly and widely [Smith, 1996]. The median time from diagnosis to metastases is 35 months.

Treatment involves the wide surgical excision of the tumor and surrounding tissue and high grade round cell liposarcoma may be treated with pre-operative chemotherapy and/or pre- operative or post-operative radiotherapy [NCCN, 2012).] Radiotherapy decreases the incidence of local relapse but chemotherapy may not prevent metastatic occurrence and improve survival [Moreau, 2012; Hoffman, 2013].

Doxorubicin and ifosfamide are usually first line treatment options for metastatic disease. Retrospective analyses in previously untreated patients demonstrated response rates of ~38 - 45% [Jones, 2005; Katz, 2012]. In a retrospective analysis of trabectedin in advanced pre-treated MRCLS (in which 46 of the 51 patients had received anthracycline and ifosfamide either in combination or in sequence), a response rate of 51% was reported [Grosso, 2007]. A randomized, open-label, active-controlled trial comparing trabectedin (n=345) treatment with dacarbazine (n=173) in patients with unresectable, locally advanced or metastatic leiomyosarcoma (73%) or liposarcoma (27%) (dedifferentiated, myxoid round cell, or pleomorphic) and previous treatment with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen demonstrated an overall response rate (ORR of 7% (CI 4.3, 9.8) with trabectedin, an improvement of median progression-free survival (PFS) of 4.2 (CI 3.0, 4.8) vs 1.5 (CI 1.5, 2.6) months on dacarbazine but no difference in overall survival (YONDELIS 2015 prescribing information). Eribulin demonstrated an improvement in survival (median OS 13.5 vs 11.5 months; HR= 0.768; 95% CI, 0.618; 0.954) compared with darcarbazine in subjects with liposarcoma and leiomyosarcoma who received 2 or more prior lines of therapy. There was no difference in PFS and ORR was 3.9% with Eribulin and 4.9% with darcarbazine [Schöffski, 2015].

1.4. Rationale for NY-ESO-1^{c259}T for Myxoid/ Round Cell Liposarcoma

Subjects with MRCLS who relapse after anthracycline-based therapy have few therapeutic options. The occurrence of diffuse and high intensity expression of NY-ESO-1, the anti-tumor activity of NY-ESO-1^{c259}T in synovial sarcoma, combined with a manageable safety profile is the basis of this clinical trial designed to evaluate the activity and safety in myxoid/round cell liposarcoma (MRCLS). NY-ESO-1^{c259}T has not previously been used for the treatment of MRCLS, therefore this pilot study will evaluate safety and efficacy in this indication.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Trial Objectives and Endpoints

Table 1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy 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 subjects with NY-ESO-1 expressing advanced myxoid/ round cell liposarcoma	• Overall Response Rate[1] (ORR) per RECIST v1.1 by investigator assessment
Secondary	
To evaluate the efficacy 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 subjects with NY-ESO-1 expressing advanced myxoid/ round cell liposarcoma	• Overall Response Rate[1] (ORR) per RECIST v1.1 by independent review • Time to Response[2] • Duration of Response[2] • Progression Free Survival[2]
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 subjects with NY-ESO-1 expressing advanced myxoid/ round cell liposarcoma	• AEs, including SAEs and AESIs • Laboratory assessments, including chemistry and hematology • Replication competent lentivirus (RCL) • Instances of insertional oncogenesis • Incidence of anti-NY-ESO-1^{c259}T antibodies • ECG
To characterize the in vivo PK profile (levels, expansion, persistence) of NY-ESO-1 specific (c259) cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

[1]Overall Response Rate is based on confirmed responses determined at least 4 weeks post initial identification of response.
[2]Secondary response endpoints may be based on investigator assessment and independent review.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase I/II open label pilot study of genetically engineered NY-ESO-1c259 T in HLA- A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive subjects with NY-ESO-1 expressing advanced (metastatic or inoperable) cytogenetically confirmed myxoid/ round cell liposarcoma. Inoperable refers to a tumor lesion in which clear margins cannot be obtained without leading to significant functional compromise. A maximum of 20 subjects will be treated/infused on this study.

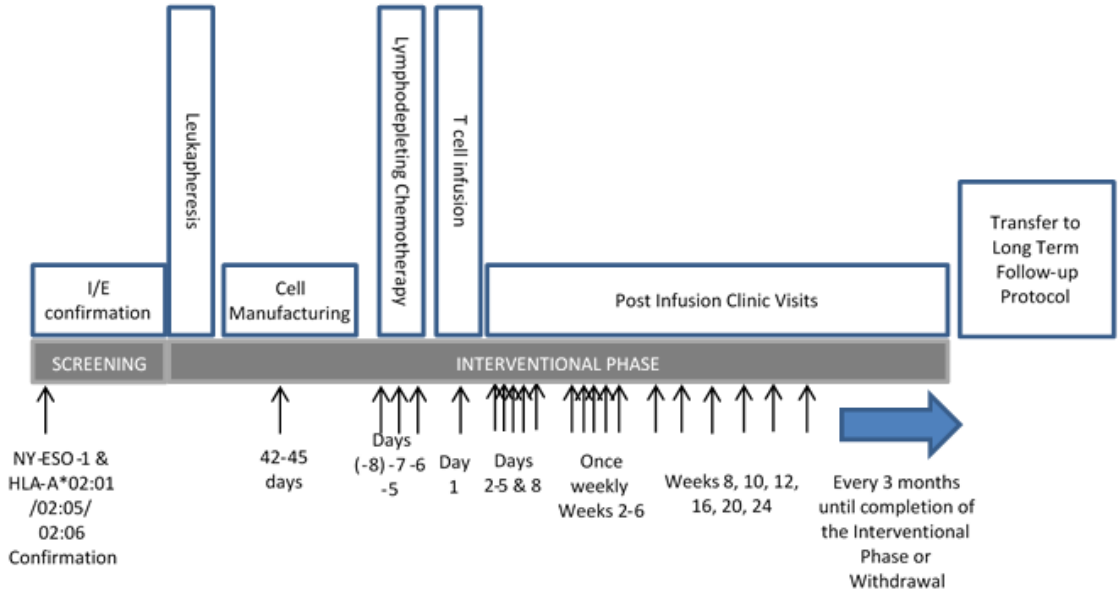
Subjects will be screened for the presence of HLA-A*02:01, HLA-A*02:05, HLA-A*02:06 and NY-ESO-1 expression on the tumor (Section 7.1). The Screening Phase of the study starts from the time the subject signs the study Screening Informed Consent Form until the subject attends for second screening following antigen positivity. The subject then signs the Treatment Informed Consent Form prior to any further study tests or procedures and transfers to the Interventional Phase of the study which runs from the time of treatment consent until disease progression, death or 2 years after NY-ESO-1^{c259}T cell infusion, whichever is shorter (completion of the interventional phase, see Section 4.3). NY-ESO-1^{c259}T cell infused subjects alive on completing or withdrawing from the interventional phase will continue to be monitored in one of two ways: either via transfer to the Long Term Follow-Up (LTFU) protocol GSK208750 (ADP 0000-002) to monitor for gene therapy related delayed adverse events for 15 years, in accordance with regulatory requirements for gene therapy clinical trials; or via continuation in the current trial until the LTFU protocol is available. If necessary and upon discussion with the Sponsor, those patients who have not progressed after 2 years on study and who are continuing in Study 208469 may continue to undergo response assessments every 3 months as defined in Study 208469 per institutional standard of care.

Subjects will be screened for enrolment into the study according to the eligibility criteria in Section 4. Following enrolment, subjects will undergo leukapheresis for collection of autologous cells for processing and manufacture into the NY-ESO-1^{c259}T cell investigational product. Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation.

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 are available, subjects will undergo lymphodepleting chemotherapy with cyclophosphamide and fludarabine (Section 5.2) followed by infusion of NY-ESO-1^{c259}T cells (Section 5.3) on Day 1. Lymphodepletion may be given as outpatient treatment. The T cell infusion should be given as an inpatient procedure. Subject may be hospitalized for follow-up care post T-cell infusion at the discretion of the investigator. Subjects will receive growth factor support with Granulocyte Colony Stimulating Factor (G-CSF) from 24 hours following lymphodepleting chemotherapy until neutrophil count recovery.

Efficacy, safety, and biomarker assessments to be conducted at each visit are outlined in the Schedule of Procedures (Table 4). Efficacy will be assessed by local and independent review using RECIST v1.1 criteria as described in Section 7.4.9 and Section 16.4. 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.

Figure 1 Schematic for Study GSK208469



3.2. Components of Study Design

3.2.1. Study Phases

The study is divided into Screening and Interventional phases. The screening phase evaluates subjects for HLA type and tumor antigen expression. Subjects enter the Screening phase on signing the screening consent form at Visit 1.

If the subject screens positive for the relevant HLA alleles and has adequate tumor antigen expression, they may enter the interventional phase of the study which contains all other study tests and procedures. Subjects enter the Interventional phase on signing the treatment consent form at Visit 2 and remain in this phase until completion or withdrawal, as described in Section 4.3 and Section 4.4.

3.2.2. Screening for HLA and NY-ESO-1

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; therefore, this protocol will select for subjects with these three HLA-A2 allelic variants and whose tumor expresses the NY-ESO-1 antigen.

The prevalence of HLA sub-types varies between populations. Information on the prevalence of HLA-A2 allelic variants in specific populations 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 subject population at their site.

3.2.3. T-Cell Manufacturing

GSK3377794 is the first generation product consisting of autologous T cells transduced with lentiviral vectors to express the affinity enhanced TCR (c259) and is currently being investigated in ongoing GSK sponsored pilot clinical trials in HLA-A*02+ participants with NY-ESO-1 and/or LAGE-1a positive metastatic synovial sarcoma (SS) (208466 [ADP-04511]), advanced myxoid/ round cell liposarcoma (MRCLS) (study 208469 [ADP-0011-007]), non-small cell lung cancer (NSCLC) (GSK study 208749 [ADP-0011-004] and GSK study 208471), and relapsed refractory multiple myeloma (MM) (study 208470 [ADP-0011-008]).

Adoptive T-cell therapy (ACT) is a therapeutic approach that uses a cancer patient's own T lymphocytes obtained by leukapheresis, genetically engineered to express a tumor-targeting receptor, such as a T-cell receptor (TCR) or a chimeric antigen receptor (CAR), expanded ex vivo and re-infused into the participant, with the aim of generating and propagating an anti-tumor T-cell immune response.

NY-ESO-1 and LAGE-1a are members of the cancer-testis family of tumor antigens (CTAs). NY-ESO-1 is a cytoplasmic protein that is detectable in multiple cancer types including non-small cell lung cancer (NSCLC), bladder cancer, melanoma, liver cancer, synovial sarcoma, myxoid/round cell liposarcoma (MRCLS), and many others. Specific peptide epitopes of the NY-ESO-1 or LAGE-1a protein are processed and presented on the surface of the tumor cell in complex with an HLA molecule, which can be recognized by T cells. An HLA-A*02 binding peptide ($SLLMWITQC_{aa\ 157\text{-}165}$) that is common to both NY-ESO-1 and LAGE-1a antigens has been identified that can be recognized by NY-ESO-1 reactive T cells. The T cells for therapy have been genetically engineered to express an affinity-enhanced TCR toward the SLLMWITQC peptide bound to HLA-A*02. The retained optimized TCR clone was called NY-ESO-1c259 or c259. The T-cell product consists of autologous T cells transduced with a self-inactivating lentiviral vector encoding the affinity enhanced NY-ESO-1 specific TCR (c259).

Selected qualified manufacturing sites will prepare the expanded T cells for subjects enrolled at all sites. Utilizing anti-CD3/CD28 mAb coated magnetic beads, T cells are enriched, activated and expanded in a closed system (12-14 days). T cells are then transduced with the lentiviral vector. The manufacturing process initiates in a static tissue culture bag, followed by transfer to a Wave bioreactor for additional expansion under perfusion conditions. At the end of the culture, cells are depleted of magnetic beads, washed, concentrated, and cryopreserved. Release testing takes approximately an additional 4 weeks. Therefore, cell product typically is ready to be returned to the site approximately 42-45 days after subject apheresis. Shipment to clinical sites will ideally be before the start of lymphodepleting chemotherapy, exceptions will 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, NK or B cells. By the end of the culture period, B cells comprise approximately < 2%, NK cells comprise approximately < 2%, and macrophages approximately < 1% of the total culture. Additional details are provided in the NY-ESO-1^{c259}T Investigator Brochure.

3.2.4. Lymphodepletion

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

Recent evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia and acute leukemia using adoptive cellular therapy including a chimeric antigen receptor showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in to a previously cyclophosphamide-only preparative regimen [Turtle, 2016]. Based on the results from our previous clinical research using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy and the increasing evidence that fludarabine may be a necessary component, the lymphodepleting regimen in this study consists of fludarabine 30mg/m^2/day and cyclophosphamide 600mg/m^2/day intravenously for three consecutive days. This regimen will be used for the first 10 subjects (Cohort 1). Based on emerging data and analysis, the lymphodepleting regimen for the subsequent 10 subjects (Cohort 2), if expanded, was changed to fludarabine 30mg/m^2/day for 4 days and cyclophosphamide 900mg/m^2/day intravenously for 3 days, beginning on day -8. Age related modifications to the lymphodepletion regimen will be made as outlined in Section 5.2.

3.2.5. 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 (see Section 5.3 for administration details).

3.2.6. 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 adverse events (e.g., cytokine release). Total T cell doses up to ~100 x 10^9 cells [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) cells may also be effective [Porter, 2011].

Current experience with NY-ESO-1^{c259}T is with total cell doses in the range of ~<1 – 15 x 10^9 transduced cells with a transduction level of ~18 – 75%.

The dose of NY-ESO-1^{c259}T will be within the range of 1 x 10^9 – 8 x 10^9 transduced cells, which will be administered by a single intravenous infusion on Day 1. The minimum transduced cell dose is 1 x 10^9 cells. If the manufactured transduced cell dose is less than the minimum dose, 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 total dose in the target range.

3.3. Target Enrolment and Study Duration

A target of 10 subjects infused with potential expansion up to 20 subjects is considered appropriate for evaluating preliminary efficacy (antitumor activity) and safety in this phase I/II study of subjects with a rare, orphan disease.

Potential subjects will first sign a screening consent to screen for HLA and antigen testing. It is expected that approximately 50% of subjects will be HLA negative, and 20% of these subjects will be NY-ESO negative. Therefore, it is expected that up to 60 subjects may sign the screening consent. Once HLA and antigen testing are confirmed, subjects will return for the second screening visit, at which time the treatment consent will be signed, and the remainder of eligibility requirements will be verified. Enrolled subjects will be considered those subjects who sign the treatment consent, meet all eligibility requirements, and undergo apheresis. Based on information gathered from the pilot sarcoma study, it is expected that there will be some subjects who undergo apheresis but do not receive manufactured cells. Therefore, in this study, approximately 26 subjects may be enrolled in order to obtain the target number of 20 subjects treated with manufactured product. Up to 13 subjects may be enrolled in order to obtain the target number of 10 subjects treated with manufactured product in Cohort 1, and up to 13 subjects may be enrolled in order to obtain the target number of 10 subjects treated with manufactured product in Cohort 2. Once the target number of patients have manufactured product in each cohort, the study will be closed for enrolment and apheresis. In the event that a subject has manufactured product and is not able to receive treatment, an apheresis slot may then be opened for a screen positive patient to be enrolled.

Expansion from n=10 to a maximum of n=20 may be done to better characterize safety, efficacy and tolerability, based on the clinical evaluation of the emerging data (See Section 11). In addition, more subjects may be enrolled for those who do not receive the

minimum cell dose or who do not receive the T-cell infusion to better characterize safety, efficacy and tolerability as part of this expansion.

The confirmed overall response rate per RECIST v1.1 by investigator review will be evaluated after the first 10 subjects are evaluable, defined as have been treated and had at least 3 post-baseline disease assessments or have progressed or died or were withdrawn from the study.

In the event that 1 or no responses are observed in these 10 evaluable subjects from the first cohort then no further enrolment will occur.

Once 10 subjects have been enrolled screening may continue but no further subjects will enroll, undergo leukapheresis or lymphodepletion until a decision is made to expand the study. As enrolment nears 10 subjects the Sponsor and Investigators will discuss whether further screening is appropriate.

Criteria for suspending the study for safety are outlined in Section 10.2.

The study will be considered completed when the last subject has been rolled over into the LTFU protocol GSK208750 (ADP-0000-002), has completed long term follow-up in this study, has declined LTFU, has been withdrawn from study (including lost to follow-up), or died, as detailed in Section 4.3.

3.4. Sites

The study will be conducted in approximately 10 sites. The number of centers is necessary to ensure recruitment in this rare population. Additional sites 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 and risks, and the risk mitigation strategy for this study.

3.5.1. Benefit Assessment

The NY-ESO-1 cancer testis antigen is expressed in 80% of patients with MRCLS [Endo, 2015]. This is the first study to evaluate the safety and efficacy of NY ESO-1^{c259}T in MRCLS.

A patient's T cells can be genetically engineered to recognize tumor antigens. The TCR approach to engineered T cell therapy is attractive because TCRs are capable of recognizing not only cell surface proteins (as is the case with CARs) but also any internal protein, since TCRs recognize peptide fragments in the context of HLA. In addition, the TCR approach 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.

Objective responses have been observed in subjects with sarcoma, myeloma and melanoma [Robbins, 2015; Rapoport, 2015; D'Angelo, 2015]. In subjects with unresectable synovial sarcoma, 12 subjects were treated with NY-ESO-1^{c259}T and six responded (1 CR and 5 PR). Median duration of response was more than 6 months [D'Angelo, 2015]. In the NCI sponsored trial, 11 of 18 subjects (61%) with synovial sarcoma demonstrated objective clinical responses. The estimated overall 3- and 5-year survival rates for patients with synovial sarcoma were 38% and 14% respectively [Robbins, 2015].

MRCLS and synovial sarcoma share certain similarities in that they are both translocation sarcomas with a high intensity NY-ESO-1 antigen expression. The efficacy observed in synovial sarcoma supports the investigation of NY ESO-1^{c259}T cells in patients with MRCLS.

3.5.2. Risk Assessment

The known safety profile of NY ESO-1^{c259}T is updated annually in the Investigator Brochure. Current AEs are based on N=103 subjects enrolled as of January 2020. All subjects (100%) experienced at least 1 TEAE after infusion with GSK3377794 (letestregene autoleucel; lete-cel). Most subjects (98%) had at least one Grade 3 AE; in 83% of the subjects, the Grade 3 AEs were considered by the investigator to be related to GSK3377794 treatment. TEAEs which occurred in >50% of all subjects following GSK3377794 infusion were nausea (80%), anemia/RBC decreased (79%), neutropenia/neutrophil count decreased (79%), leukopenia/WBC decreased (78%), pyrexia (74%), thrombocytopenia/platelet count decreased (74%), fatigue (73%), diarrhea (57%), lymphopenia/lymphocyte count decreased (53%), and decreased appetite (50%). Grade 3 and 4 AEs which occurred in >50% of all subjects following GSK3377794 infusion were leukopenia/WBC decreased (75%), neutropenia/neutrophil count decreased (71%), thrombocytopenia/platelet count decreased (59%),anemia/RBC decreased (57%), and lymphopenia/lymphocyte count decreased (50%). There has been one report of fatal bone marrow failure after initial bone marrow recovery.

There have been 31 reports of CRS (grades 1-4) from subjects who received NY-ESO-1^{c259}T cells, all of which resolved. Twenty-nine subjects had CRS following a single infusion of NY-ESO-1^{c259}T cells and 4 out of 15 subjects had CRS after their second infusion. Onset of CRS symptoms typically occurs within 2 weeks from the T-cell infusion, coinciding with maximal in vivo T-cell expansion.

Overall, GvHD (grades 1-3, including GvHD in gastrointestinal tract and GvHD in skin) has been reported in 7 subjects who received NY-ESO-1^{c259}T cells, and all cases have resolved. All 7 subjects had multiple myeloma: 6 subjects (Study ADP-01411/NCT01352286) had previously undergone ASCT, while the 7th subject (Study 208470) had not. Although there is a probable association with autologous stem cell

transplant, symptoms such as rash, colitis and diarrhea have been reported in other NY-ESO-1^{c259}T studies.

The Investigator Brochure contains detailed safety information (GSK Document Number RPS-CLIN-024388.

To manage the risk of CRS and GvHD in the NY-ESO-1^{c259}T program, GSK is implementing specific AE pages in the electronic case report form (eCRF) to carefully document the events and to enable evaluation and identification of potential risk factors. To help Investigators manage CRS and GvHD, GSK has developed treatment guidance based on published literature which is included in the protocol (see Section 8). Study sites are expected to have access to physicians with expertise in bone marrow transplantation 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.

Sponsor is also 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, 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.

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

Acute inflammatory demyelinating polyneuropathy / Guillain Barré Syndrome (GBS) developed in two subjects who received the NY-ESO-1C259T 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 treatment until further investigation.

Potential risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been 2 reports of unexpected cardiac arrest. The first occurred 5 months after T-cell infusion and was confounded by hypotension due to poor oral intake and concurrent renal insufficiency. The second occurred approximately 1 week after T-cell infusion in the setting of a recent fungal catheter line infection, concurrent treatment with caspofungin and multifocal pneumonia / edema seen on chest CT. Participants with significant cardiac risk factors or with CRS ≥ Grade 2 will receive close cardiac monitoring (Section 7.4.8). Participants with lung metastases should be considered for pulmonary consultation prior to lymphodepletion; participants deemed at high risk of pulmonary complications should

be monitored closely (Section 7.4.9). Central lines should be closely monitored for infection (Section 8.2). Systemic fungal infections are excluded (Exclusion 9) Monitoring of risk of increased cardiac toxicity with the use of anti-microbials (Core Section 8.2.6)

Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been reports of haemorrhage (including intracranial and pulmonary) in participants with severe prolonged thrombocytopenia. Protocol guidance on Blood product support provides recommendation on platelets levels to be maintained in the in-patient setting and the out-patient setting, as per Section 8.3

Additional experience in clinical trials is required to confirm the incidence of these and other risks. The goal of the risk mitigation strategies 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

Data from preclinical studies support the efficacy, specificity, and safety of NY-ESO-1^{c259}T cells (Investigator Brochure). Clinical data from subjects summarized in the Investigator Brochure and the NCI study [Robbins, 2015] demonstrate the safety and activity of NY-ESO-1^{c259}T sufficiently to support the clinical investigation of this product in MRCLS. The design of the study aims to evaluate the overall benefit:risk of using the treatment in a new indication by evaluating efficacy and safety in an initial pilot study.

4. SELECTION OF STUDY POPULATION

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

4.1. Subject Inclusion Criteria

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

1. Subject (or legally authorized representative) 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 at the time of signing the study informed consent
4. Subject has a diagnosis of high grade myxoid liposarcoma / myxoid round cell liposarcoma confirmed histologically and by the presence of the reciprocal chromosomal translocation t(12;16) (q13;p11) or t(12; 22) (q13;q12).

5. Subject has advanced (metastatic or inoperable) high grade myxoid liposarcoma / myxoid round cell liposarcoma. Inoperable refers to a tumor lesion in which clear margins cannot be obtained without leading to significant functional compromise
6. Subject has measurable disease according to RECIST v1.1 criteria.
7. Subject must be HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive.
8. Subject's tumor (either the most recent archival specimen or a fresh biopsy) shows positive NY-ESO-1 expression defined as ≥30% of cells that are 2+ or 3+ by immunohistochemistry. All samples must have been pathologically reviewed by a GSK designated central laboratory.
9. Subject must have previously received or be intolerant to anthracycline based therapy for advanced (metastatic or inoperable) disease. Subjects who received neoadjuvant/adjuvant anthracycline based therapy and progressed within 6 months of completion of therapy will be eligible.
10. Subject has an ECOG Performance Status 0-1.
11. Subject has a left ventricular ejection fraction ≥45%.
12. Subject is fit for apheresis 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.

    - 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 (WOCBP) 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:

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

- Is not a WOCBP as defined in Section 6.3.1

  OR

- Is a WOCBP (as defined in Section 6.3.1) 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 6.3.1 during the intervention period and for at least 12 months after receiving the T-cell infusion. In the event that there is evidence of persistence/gene-modified cells in the participant's blood, contraception usage should continue until 2 consecutive persistence tests show that GSK3377794 is below the level of detection in blood. 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.

14. Subject must have adequate organ function as indicated by the laboratory values in the table below:

System	**Laboratory Value**
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.5 x10^9/L (without G-CSF support)
Platelets	≥ 100 x10^9/L
Hemoglobin	≥ 80 g/L (without transfusion support within 7 days prior to leukapheresis)
Coagulation	
Prothrombin Time or INR	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Partial Thromboplastin Time (PTT)	≤ 1.5x upper limit of normal (ULN) unless receiving therapeutic anticoagulation.
Renal	
Calculated or measured creatinine clearance 1	≥ 40 mL/min

1

- Participants who are ≥18 and <65 years of age must be assessed either:
  - by 24-hour urine creatinine collection OR
  - by using Serum Creatinine (Scr) via an estimated creatinine clearance (CrCl) calculated as outlined below by using the Chronic kidney disease Epidemiology Collaboration (CKD-EPI) equation and adjusting the result by multiplying with (Body Surface Area [BSA]/1.73) to obtain a CrCl in mL/min.

  Step 1: estimated glomerular filtration rate (GFR) to be obtained from the CKD-EPI formula [Levey, 2009]:

  Estimated GFR (mL/min/1.73m^2) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 *[if female]* × 1.159 *[if black]*

  where:

  Scr is serum creatinine in mg/dL,
  κ is 0.7 for females and 0.9 for males,
  a is -0.329 for females and -0.411 for males,
  min(Scr/κ,1) indicates the minimum of Scr/κ or 1,
  max(Scr/κ,1) indicates the maximum of Scr/κ or 1, and
  Age is in years.

  Step 2: correction factor to be applied per the American National Kidney Foundation in order to obtain the estimated creatinine clearance in mL/min

  Estimated CrCl (mL/min) = Estimated GFR (mL/min/1.73 m^2) × BSA (m^2) / 1.73

  To calculate the BSA for fludarabine dosing, use actual body weight. An adjusted body weight may be required for cyclophosphamide, refer Section 5.2.2. for further details.

- Participants ≥65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine ethylenediaminetetraacetic acid (EDTA) GFR measurement, according to standard practice at the treating institution

4.2. Subject Exclusion Criteria

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

1. Subject has received or plans to receive the following excluded therapy/treatment within the following periods prior to leukapheresis or lymphodepleting chemotherapy:

Treatment/Therapy	**Required Wash-out Prior to Leukapheresis**	**Required Wash-out Prior to Lymphodepletion**
Cytotoxic chemotherapy	3 weeks	3 weeks
Small Molecules/Tyrosine kinase inhibitor (TKI) such as pazopanib.	1 week	1 week
Treatment/Therapy	Required Wash-out Prior to Leukapheresis	Required Wash-out Prior to Lymphodepletion
Immune therapy (including monoclonal antibody therapy, checkpoint inhibitors, biologics)	2 weeks	2 weeks
Experimental anti-cancer Vaccine	2 months in the absence of tumor response, or the subject should be excluded if their disease is responding to an experimental vaccine given within 6 months	2 months in the absence of tumor response, or the subject should be excluded if their disease is responding to an experimental vaccine given within 6 months
Gene therapy using an integrating vector	Any use of previous gene therapy using an integrating vector is not permitted	Any use of previous gene therapy using an integrating vector is not permitted
Allogeneic hematopoietic stem cell transplant (HSCT)	Any allogeneic HSCT is not permitted	Any allogeneic HSCT is not permitted
Corticosteroids or any other immunosuppressive therapy. Use of topical steroids is not excluded.	2 weeks	2 weeks
Investigational treatment	4 weeks	4 weeks
Duration of any other anti-cancer therapies must be discussed with the Sponsor Study Physician		

2. Radiotherapy within the following periods prior to leukapheresis or lymphodepleting chemotherapy (Participant has received ≥50 Gy to a significant volume of the pelvis, long bones or spine, or a cumulative dose of radiation that, in the investigator's opinion would predispose patients to prolonged cytopenia after lymphodepletion):

Treatment/Therapy	**Required Wash-out Prior to Leukapheresis**	**Required Wash-out Prior to Lymphodepletion**
Radiotherapy that involves the lung (V20 exceeding 30% lung volume) or pericardium (>20Gy). Exception for a lesser dose or radiation exposure to lung/mediastinum than stated, administered within 4 weeks prior to lymphodepletion. Electron beam radiotherapy to superficial structures in the chest is permitted.	N/A	3 months

Treatment/Therapy	**Required Wash-out Prior to Leukapheresis**	**Required Wash-out Prior to Lymphodepletion**
Radiation to vital organs (e.g., liver, kidney)	N/A	4 weeks
Radiation to the pelvis	4 weeks	4 weeks
Whole Brain Radiotherapy (WBRT) or Brain Stereotactic Radiosurgery (SRS)	N/A	2 weeks
Radiotherapy to the target lesions	N/A	3 months prior to lymphodepleting chemotherapy. A lesion with unequivocal progression may be considered a target lesion. There is no washout period for palliative radiation to non-target organs.

3. Subject that has toxicity from previous anti-cancer therapy must have recovered to ≤ Grade 1 (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g., peripheral neuropathy) can be enrolled.

4. Subject has history of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study.

5. Subject has history of chronic or recurrent (within the last year prior to screening) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments.

6. Subject has known active brain or leptomeningeal metastases. Subjects with prior history of brain metastasis who have undergone local therapy (i.e., metastasectomy 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 prior malignancy that is not in complete remission.

8. Subject has electrocardiogram (ECG) showing clinically significant abnormality at Screening or an average QTc interval (Fridericia's or Bazett's formula) >450 msec in males and >470 msec in females (>480 msec for subjects with Bundle Branch Block (BBB)).

9. Subject has uncontrolled intercurrent illness including, but not limited to:

   - Ongoing or active infection including but not limited to systemic fungal infection; EBV and CMV IgG seropositive patients who have a positive PCR

- Prior or active demyelinating disease
- Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4
- Uncontrolled clinically significant arrhythmia in last 6 months
- Acute Coronary Syndrome (ACS) (angina or MI) in last 6 months
- Interstitial lung disease (subjects with existing pneumonitis as a result of radiation are not excluded, however, subjects must not be oxygen dependent).

10. Subjects who in the opinion of the Investigator will be unlikely to fully comply with protocol requirements.
11. **ALT**>2.5 times ULN without documented liver metastases/tumor infiltration

    OR

    Total Bilirubin > 1.5 x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
12. Subject has active infection with HIV, HBV, HCV or HTLV as defined below:
    - Positive serology for HIV
    - Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation.
    - Active hepatitis C infection as demonstrated by test for hepatitis C RNA. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value
    - Positive serology for HTLV 1 or 2.

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

4.3. Completion of the Interventional Phase

A NY-ESO-1^{c259}T infused subject will be considered to have completed the interventional phase of the study when he/she has progression of disease (see Section 7.4.11 for tumor response assessments), death, or has been followed-up for 2 years after NY-ESO-1^{c259}T cell infusion, whichever is shorter.

All NY-ESO-1^{c259}T infused subjects alive on completing or withdrawing from the interventional phase will continue into long-term follow-up (LTFU) for observation of delayed adverse events as described in Section 7.4.12. If necessary and upon discussion with the Sponsor, those patients who have not progressed after 2 years on study and who are continuing in Study 208469 may continue to undergo response assessments every 3 months as defined in Study 208469 per institutional standard of care.

This study will be considered complete when the last subject has been rolled over into the LTFU protocol GSK208750 (ADP-0000-002), has completed long term follow-up in this study, has declined LTFU, has been withdrawn from study (including lost to follow-up), or died.

4.3.1. Long-Term Follow-up

All participants will be followed for survival and for 15 years after T-cell (GSK3377794) infusion to permit observation of delayed AEs in accordance with FDA requirements for gene therapy clinical trials [FDA Guidance, 2006b; FDA Guidance, 2010; FDA Guidance, 2020]. 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 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

4.4. Subject Withdrawal

A subject may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or institution. However, the Investigator must make every reasonable effort to keep each subject on study for the whole duration of the trial. In cases where the subject is deemed ‘lost to follow-up’, the investigator or designee must make every effort to regain contact with the subject; e.g., 3 documented attempts, one of which must be a certified letter to the subject’s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject’s

medical records. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with the primary reason as 'Lost to Follow-up'.

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 electronic Case Report Form (eCRF). The following are justifiable reasons for the investigator to withdraw a subject from study:

- Subject withdraws consent.
- Initiation of alternative anti-cancer therapy with no plans to initiate treatment with NY-ESO-1^{c259}T cells

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 pharmacogenetic 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, 'adverse event (AE)' will be recorded as the primary reason for permanent 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 the Schedule of Procedures Table (see Section 7.3).

5. STUDY TREATMENTS

5.1. Leukapheresis

Subjects who complete screening procedures defined in Section 7 and who meet eligibility criteria defined in Section 4 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 ≥ 0.5 x 10^9/L and a CD3 lymphocyte count ≥ 0.2 x 10^9/L is recommended. For collection of starting material, a large-volume non-mobilized PBMC collection should be performed according to institutional standard procedures. 2 -3 blood- volumes should be processed per procedure with a goal of the procedure being collection of 1.0 x 108 PBMC/kg body weight, and a minimum of 1.5 x 107 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 against adverse effects of citrate anticoagulant (e.g., CaCl2 infusions) should 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 eligible subjects will proceed to have lymphodepleting chemotherapy and infusion of the study therapy as detailed in Section 5.2 and Section 5.3.

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 and have fulfilled release criteria, fludarabine and cyclophosphamide will be used as lymphodepleting chemotherapy prior to administration of the study treatment as described in Section 5.3. Appropriate IV hydration should be administered and Mesna given to prevent urotoxicity while cyclophosphamide is administered, according to institutional guidelines; a suggested schedule is shown in Section 5.2.2. Other premedication (e.g., anti-emetics) may also be provided in accordance with institutional standards. Steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than Day -3. G-CSF should be given to all subjects from 24 hours after the last dose of cyclophosphamide until resolution of neutropenia in accordance with ASCO guidelines or institutional practice (see Section 8.7.1).

> Dose and regimen for lymphodepleting chemotherapy is adjusted for participants ≥60 years of age, as specified in Table 2, Option 2. The investigator must discuss with the Sponsor's Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in situations such as but not limited to the following:

- Participants with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia),

- Participants with 3 or more prior lines of therapies

-Participants with documented extensive prior radiation of the pelvis, long bones or spine

- Participants with documented history of intensive chemotherapy that could reduce the bone marrow reserve

- Participants with documented low albumin (≤3.5 g/dL)

On admission for lymphodepleting chemotherapy subjects should commence antimicrobial and antifungal prophylaxis in line with ASCO Guidelines [Flowers, 2013] or institutional standard practice (see Section 8.2).

Table 2 Treatment Schema

Lymphodepleting chemotherapy (Option 1: First 10 Subjects)					**Recommended supportive medication**
Day	**Drug**	**Dose**	**Route**	**Administration [5]**	**Hydration**: Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions **Mesna**: may be given per institutional guidelines or as recommended in Section 5.2.2 **G-CSF**: start 24 hours post final cyclophosphamide until resolution of neutropenia[3] **Cell therapy premedication**: premedication with acetaminophen and diphenhydramine should be given 30 - 60 minutes prior to the NY-ESO-1^{c259}T infusion according to institutional practice
-7	Fludarabine[1]	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins [4]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-6	Fludarabine[1]	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins [4]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-5	Fludarabine[1]	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins [4]	
	Cyclophosphamide	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-4	start G-CSF				
-3					
-2					
-1					
1[6]	NY-ESO-1^{c259}T infusion[2]				

NS = Normal Saline

1. Fludarabine dose will be adjusted in renal impairment as described in Section 5.2.1
2. Administration of NY-ESO1^{c259}T infusion is described in Section 5.3
3. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose 24 hours after the last chemotherapy administered
4. Concentration ≤1mg/mL
5. Or per institutional guidelines
6. There is no Day 0; T cell infusion takes place on Day 1

Lymphodepleting chemotherapy (Option 2: Based on emerging data)						**Recommended supportive medication**
Day	**Drug**	**Dose**	**Dose for participants ≥60 years old**	**Route**	**Administration [5]**	**Hydration**: Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions **Mesna**: may be given per institutional guidelines or as recommended in Section 5.2.2 **G-CSF:** start 24 hours post final cyclophosphamide until resolution of neutropenia[3] **Cell therapy premedication**: premedication with acetaminophen and diphenhydramine should be given 30 - 60 minutes prior to the NY-ESO-1^{c259}T infusion according to institutional practice
-8	Fludarabine[1]	30 mg/m^2	none	IV	in 50 – 100 ml 0.9% NaCl over 30 mins [4]	
-7	Fludarabine[1]	30 mg/m^2	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins [4]	
	Cyclophosphamide	900 mg/m^2	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-6	Fludarabine[1]	30 mg/m^2	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins [4]	
	Cyclophosphamide	900 mg/m^2	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-5	Fludarabine[1]	30 mg/m^2	30 mg/m^2	IV	in 50 – 100 ml 0.9% NaCl over 30 mins [4]	
	Cyclophosphamide	900 mg/m^2	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 1 hour	
-4	start G-CSF					
-3						
-2						
-1						
1 [6]	NY-ESO-1^{c259}T infusion[2]					

NS = Normal Saline

1. Fludarabine dose will be adjusted in renal impairment as described in Section 5.2.1. Fludarabine dose will not be adjusted by body weight per American Society for Blood and Marrow Transplantation (ASBMT) guidelines that recommend dosing based upon BSA using total body weight [Bubalo, 2014], unless required otherwise by institutional guidelines
2. Administration of NY-ESO1^{c259}T infusion is described in Section 5.3
3. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose 24 hours after the last chemotherapy administered
4. Concentration ≤1mg/mL
5. Or per institutional guidelines
6. There is no Day 0; T cell infusion takes place on Day 1

5.2.1. Fludarabine Dose Adjustment for Renal Impairment

This adjustment needs to be applied for patients treated under either Option 1 or Option 2. Patients ≥ 60 years of age receiving an age-adjusted dose will have the renal adjustment applied to the modified dose for age. Dose of fludarabine will be adjusted for subjects with renal dysfunction as follows:

Table 3 Fludarabine dose adjustment

Creatinine clearance	Fludarabine dose
≥80mL/min	30 mg/m^2
>50 – 80 mL/min	20 mg/m^2
30 – 50 mL/min	15 mg/m^2

Note: to estimate CrCl (in mL/min) please use Section 4.1 Inclusion 14 for calculation steps before comparing to the thresholds given above.

If estimating CrCl using the CKD-EPI equation, adjust the result by multiplying with (BSA/1.73) to obtain a CrCl in mL/min. For fludarabine dosing, to calculate BSA, use actual body weight.

Creatinine clearance must be reassessed prior to lymphodepletion for use in these calculations.

5.2.2. Cyclophosphamide Dose Adjustment

This adjustment needs to be applied to all doses, on top of the age-related modification. If the participant's weight is greater than 175% Ideal Body Weight (IBW), then calculate cyclophosphamide dose based on BSA calculated using the Adjusted Body Weight (ABW).

These adjustments need to be applied on top of any age-related or tumour-related modifications.

Calculating Ideal Body Weight

	Estimated IBW in Kg
Males	IBW = (0.9 x Height in cm) - 88
Females	IBW = (0.9 x Height in cm) - 92

Estimation of IBW may be performed per local institutional guidelines instead, if required.

Calculating Adjusted Body Weight

If the actual body weight is greater than 175% of the calculated IBW, calculate the ABW:

ABW = IBW + 0.4 x (actual weight - IBW)

Estimation of ABW may be performed per local institutional guidelines instead.

The IBW and ABW are used to calculate medication dosages when the participant is obese. This formula only applies to persons 152 cm or taller. Use ABW in the calculation for body surface area.

5.2.3. Mesna

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

120 mg/m^2 (20% cyclophosphamide dose) as an IV bolus at T=0, 3, 6 and 9 hours relative to cyclophosphamide administration.

5.3. T Cell Infusion

On Day 1, the subject will receive NY-ESO-1^{c259}T by intravenous infusion (please note there is no Day 0 in the schedule). Prior to infusion, two clinical personnel, in the presence of the subject, will independently verify and confirm that the information on the infusion bag label is correctly matched to the subject, as per the participating center's blood bank procedures.

Subjects will be premedicated with antihistamine and acetaminophen (paracetamol) 30-60 minutes prior to the T cell infusion according to institutional practice. Steroids must not be administered as premedication for T cell infusion.

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. The infusion should commence immediately after thawing, or immediately upon delivery to the bedside if thawed centrally and should be completed 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 of the first has been infused without reaction. The same principles should be applied to any subsequent bags.

If after thawing, the inner infusion bag is damaged or leaking, the PI 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 50ml saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided. On completion of the cell infusion the set should be flushed using additional saline from the attached bag.

In the event of adverse reaction to the cell infusion the infusion rate should be reduced and the reaction managed according to institutional standard procedures (see Section 8). 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 interests of the subject. The timing of all assessments post-infusion will be calculated with reference to the T-cell infusion date. 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, and at 1, 1.5, 2 and 4 hours after the infusion has started.

6. CONCOMITANT MEDICATION AND TREATMENT

Starting at the time the subject signs the treatment informed consent form at Visit 2, all concomitant medications taken during the study, including prescription and over-the-counter (OTC) medications and herbal remedies, will be recorded in the eCRF. Indication, dose, route and frequency will also be recorded. Any changes to concomitant medications should be recorded throughout the study in the eCRF.

The full history of prior anti-cancer therapy for each subject will be recorded in the eCRF.

6.1. Prohibited Concomitant Medication and Treatment

The following treatments are prohibited from the start of lymphodepleting chemotherapy: non- protocol chemotherapy, immune therapy, biological therapy (including targeted therapies with tyrosine kinase inhibitors or monoclonal antibodies), or investigational anti-cancer therapy.

During the interventional phase of the study until PD is confirmed subjects should also not undergo other anticancer locoregional therapies such as surgical resection, excisional biopsies or non-palliative radiotherapy.

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

The use of systemic steroids may abrogate the effects of the T cell therapy and therefore use is discouraged unless it is required to manage cytokine release syndrome (CRS) (see Section 8.5 for CRS treatment recommendations) or other significant immune-mediated adverse events. According to local standard of care, steroids may be used as anti-emetics for cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the IP (Day -3). Topical cutaneous steroids and inhaled steroidal treatments are permitted.

6.2. Permitted Concomitant Medication and Treatment

Lesion sites previously requiring radiotherapy should be recorded prior to lymphodepletion.

Palliative radiation for pain relief to non-measurable lesions or non-target lesions present at baseline is permitted during the study. However, lesion sites requiring radiotherapy after the

T-cell infusion should be evaluated to determine if the need is due to disease progression rather than pain palliation.

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 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) with a live vaccine, consult an infectious disease specialist or clinical practice guidelines (e.g., CDC Clinical Practice Guidelines for Vaccination of the Immunocompromised Host). Before immunizing a subject against SAR-CoV-2 (COVID-19) it is requested that you contact the study Sponsor.

6.3. Restrictions

6.3.1. 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

- Premenarchal
- 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.

- 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 enrolment.

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 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 below from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the intervention period up to 12 months after receiving T -cell infusion. In the event that there is evidence of persistence/gene-modified cells in the participant's blood, contraception usage should continue until 2 consecutive persistence tests show that GSK3377794 is below the level of detection in blood. 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.

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. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) 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 (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study.

If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

The IB and Informed consent also contain language describing the risks and contraceptive guidelines described above.

7. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The Schedule of Procedures for the study is provided in (Table 4). On completion of the Interventional Phase of this study subjects will transfer to the LTFU protocol (GSK208750(ADP-0000-002)) or may be followed on the current protocol until the LTFU protocol is available. A subject will have the same Subject ID in this study (GSK208469 (ADP-0011-007)), and in the LTFU Protocol (GSK208750 (ADP-0000-002)). Refer to the SRM for further details on assignment of Subject ID.

Subjects will be assigned a unique subject number upon signing the tissue screening informed consent (Section 7.1) according to procedures outlined in the SPM. The number assigned at screening will serve as the subject ID upon qualification and enrolment into the interventional phase of the study.

Study procedures performed as part of standard of care prior to signing informed consent can be used for screening if they were performed within a medically reasonable period of time prior to signing the informed consent (see Schedule of Procedures, Table 4, for additional details).

7.1. HLA and Antigen Screening

Subjects that are identified by the investigator as possible candidates for the trial must consent to initial screening tests that will first confirm that the subject is HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive (by using high resolution HLA typing for the A locus) with NY-ESO-1 positive tumor prior to conducting the remaining study screening procedures.

Blood samples will be submitted for HLA typing at a central laboratory to determine eligibility. Prior or local HLA typing results may not be used to determine eligibility.

An archival tumor sample may be submitted for determination of NY-ESO-1 expression, in which case, the biopsy from the most current setting is preferred. If an archival specimen is unavailable, the subject must undergo a new biopsy.

The subjects' tumor will be tested for NY-ESO-1 antigen expression by immunohistochemistry (IHC) using a CLIA-certified Clinical Trial Assay (CTA). Testing will be completed at a central laboratory contracted by the Sponsor.

Additional biomarkers related to the activity of NY-ESO-1^{c259}T may also be analyzed for exploratory purposes.

7.1.1. Tumor tissue requirements

A formalin-fixed, paraffin embedded (FFPE) tumor block from the most current setting is preferred for the NY-ESO-1 test. If biopsies taken at multiple time points (i.e., primary diagnosis, progression/relapse, etc.) are available, a tissue sample from the most recent biopsy should be submitted. Any blocks submitted will be returned to the sites upon request once sufficient sample has been sectioned to conduct the NY-ESO-1 test for

inclusion into the study and the necessary validations required for the development of the regulatory approved test.

If the site is unable to send a tissue block, then tissue slides taken from a single block and serially collected may be submitted.

If no archived biopsy is available, a new biopsy, preferably from a metastatic lesion is required.

Details regarding the collection and processing of the screening biopsy, sample requirements and instructions for sample shipment to the central lab for NY-ESO-1 IHC analysis are located in the SPM.

7.2. Screen Failures

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

Screen Failure data including demographics, disease history, HLA typing, NY-ESO expression and reason for failing screening will be collected in the eCRF.

7.3. Schedule of Procedures

Table 4 Schedule of Procedures (Screening and Intervention)

	Screening [1]			**Interventional phase**																												
	Screening		Leuka-pheresis	Base Line[3]	Lymphodepleting Chemotherapy				T-cell infusion	Post-infusion Assessments																						
Visit Number	1	2	3	4	(5)[23]	5 (6)	6 (7)	7 (8)	8 (9)	9 (10)	10 (11)	11 (12)	12 (13)	13 (14)	14 (15)	15 (16)	16 (17)	17 (18)	18 (19)	19 (20)	20 (21)	21 (22)	22 (23)	23 (24)	24 (25)	Every 3 Months through Yr 2[20,25]		Completion or withdrawal [4]
Visit window										± 1 day					± 3 days					± 7 days							±14d	±14d	
Day				-14 to -9	-8	-7	-6	-5	1	2	3	4	5	8															
Week															2	3	4	5	6	8	10	12	16	20	24			
Month																										9	12	
Clinical assessments																												
Informed consent [2]	X	X																										
Inclusion/ exclusion	X	X		X																								
Demographics	X																											

	Screening [1]			**Interventional phase**																										
	Screening		Leuka-pheresis	Base Line[3]	Lymphodepleting Chemotherapy				T-cell infusion	Post-infusion Assessments																				
Disease History		X																											
Medical history		X																											
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination		X		X					X					X	X														
Prior anti-cancer therapies		X		X																									
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status		X		X										X	X	X	X		X	X		X	X		X	X	X	X	X
Vital signs / weight		X[8]		X					X[5]	X	X	X	X	X	X														X

	Screening [1]			**Interventional phase**																												
	Screening		Leuka-pheresis	Base line[3]	Lymphodepleting Chemotherapy				T-cell infusion	Post-infusion Assessments																						
Visit Number	1	2	3	4	(5)[23]	5 (6)	6 (7)	7 (8)	8 (9)	9 (10)	10 (11)	11 (12)	12 (13)	13 (14)	14 (15)	15 (16)	16 (17)	17 (18)	18 (19)	19 (20)	20 (21)	21 (22)	22 (23)	23 (24)	24 (25)	Every 3 Months through Yr 2[20,25]		Completion or withdrawal [4]				
Visit window										± 1 day					± 3 days					± 7 days								±14d	±14d			
Day				-14 to -9	-8	-7	-6	-5	1	2	3	4	5	8																		
Week															2	3	4	5	6	8	10	12	16	20	24							
Month																										9	12					
ECG[21]		X		X					X			X		X																	
Echo / MUGA		X[6]																														
Brain MRI		X[6]		X[22]	X[22]																											
CT / MRI[7]		X[6]		X													X			X		X			X	X	X	X			
HLA typing[2]	X																															
NY-ESO-1 expression (most recent	X																															

	Screening [1]			**Interventional phase**																										
	Screening		Leuka-pheresis	Base line[3]	Lymphodepleting Chemotherapy				T-cell infusion	Post-infusion Assessments																				
archival or fresh biopsy) [2]																														
Hematology		X [8]		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
Biochemistry		X [8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X
Lymphocyte Subsets		X [8]																												
Coagulation[10]		X [8]		X																										
Pregnancy test[10]		X		X			X											X			X		X	X	X	X	X	X	
Urinalysis[10]		X [8]		X																										
Infectious disease screen [11]		X																												
CMV PCR [12]				X					X						X		X		X	X										
Lipase[10]				X																										
Thyroid function tests[10]				X																										

	Screening [1]			**Interventional phase**																														
	Screening		Leuka-pheresis	Base line[3]	Lymphodepleting Chemotherapy				T-cell infusion	Post-infusion Assessments																								
Visit Number	1	2	3	4	(5)[23]	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	Every 3 Months through Yr 2[20,25]		Completion or withdrawal [4]						
						(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)	(25)											
Visit window										± 1 day					± 3 days					± 7 days								±14d	±14d					
Day				-14 to -9	-8	-7	-6	-5	1	2	3	4	5	8																				
Week															2	3	4	5	6	8	10	12	16	20	24								
Month																										9	12						
C-reactive protein (CRP)[13]				X					X			X		X	X		X															
Uric acid				X					X																								
GFR[14]		X		X																													
Vector copies (Persistence) for safety[20]									X[9]																X	X	X						
VSV-G DNA (RCL) for safety[20]									X[9]													X			X	X	X						

	Screening [1]			**Interventional phase**																												
	Screening		Leuka-pheresis	Base line[3]	Lymphodepleting Chemotherapy				T-cell infusion	Post-infusion Assessments																						
Leukapheresis[15]			X																												
Fludarabine					(X)	X	X	X																							
Cyclophosphamide						X	X	X[16]																							
NY-ESO-1^{c259}T infusion									X																						
ICE									X[24]	X[24]																					
Tumor biopsy [17]				X																	X									X	
Pharmacogenetic whole blood sample				X[18]																											
PBMC (functional assays, immuno-phenotyping)				X					X[9]			X		X	X		X			X		X							X	

	Screening [1]			**Interventional phase**																														
	Screening		Leuka-pheresis	Base line[3]	Lymphodepleting Chemotherapy				T-cell infusion	Post-infusion Assessments																								
Visit Number	1	2	3	4	(5)[23]	5 (6)	6 (7)	7 (8)	8 (9)	9 (10)	10 (11)	11 (12)	12 (13)	13 (14)	14 (15)	15 (16)	16 (17)	17 (18)	18 (19)	19 (20)	20 (21)	21 (22)	22 (23)	23 (24)	24 (25)	Every 3 Months through Yr 2[20,25]		Completion or withdrawal [4]
Visit window										± 1 day					± 3 days					± 7 days						±14d	±14d	
Day				-14 to -9	-8	-7	-6	-5	1	2	3	4	5	8															
Week															2	3	4	5	6	8	10	12	16	20	24			
Month																										9	12	
Cytokine analyses [19]				X					X[9]	X	X	X	X	X	X	X	X			X		X							
Anti-NY-ESO-1 TCR Antibodies (Immunogenicity Sample)[25]									X[9]							X		X		X		X			X	X	X	X
Exosome and ctDNA collection (liquid biopsy)				X										X			X			X								X
Vector copies (Persistence) for research				X						X		X		X	X		X			X		X						X

1. Visit 2 screening assessments should be completed within 28 days of leukapheresis unless otherwise specified below.
2. Written subject informed consent must be obtained prior to performing any protocol procedures. An initial tissue screening informed consent will be signed prior to obtaining a blood sample for HLA testing and tumor tissue for tumor antigen testing. The treatment informed consent will be signed prior to all other screening procedures.

3. Baseline assessments must be conducted < 7 days prior to lymphodepleting chemotherapy.
4. If a subject withdraws consent or completes the interventional phase, all procedures and assessments listed in the completion or withdrawal visit must be performed, unless performed within the previous 30 days.
5. Timed vital signs (temperature, pulse, respirations and blood pressure (BP) on day of T cell infusion should be taken pre-infusion, and at 5, 15 and 30 minutes (±2 minutes), and 1, 1.5, 2, and 4 hours (±5 minutes) after the infusion has started.
6. Information regarding CT/ MRI scans, ECHO/MUGA scans, performed as standard of care assessments within 4 weeks prior to screening (prior to study consent) will be acceptable. CT/MRI scans performed at Screening are for eligibility purposes only and not for response determination. Scans performed at Baseline and later timepoints will be used for response determination.
7. If a subject is found to have a clinical response by imaging, a follow-up confirmation scan must be done at least 4 weeks following the scan where response is first seen. If a response is observed at week 12 or subsequent visit, the subject should attend for confirmation scan 4 weeks later, in advance of the next scheduled scan. If suspected CRS Grade ≥2, an ECHO/MUGA is required at onset of Grade ≥2 CRS. Additional monitoring must be conducted (including inpatient continuous cardiac telemetry monitoring) for a minimum of 3 days post onset and as long as deemed necessary by the Investigator (refer to Section 8.5).
8. Within 7 days of leukapheresis. Lymphocyte subsets to include absolute CD3 count.
9. Samples to be collected Day 1 pre-infusion.
10. Additional tests may be done at any time if clinically indicated.
11. Testing for infectious disease markers is required only at Screening (Visit 2) and does not need to be repeated at Baseline to satisfy the inclusion / exclusion criteria. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA. Subjects who are HCV antibody positive must have negative HCV RNA.
12. CMV IgG seropositive subjects only
13. If cytokine release syndrome is suspected, CRP levels should be measured every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.
14. Renal function will be estimated using the Cockcroft-Gault formula at Screening (Visit 2) for all subjects. At Baseline subjects <65 years may have creatinine clearance estimated using the Cockcroft-Gault formula. Subjects ≥65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine GFR measurement according to standard practice at the treating institution.
15. Screening prior to leukapheresis will meet regional legislative requirements.
16. G-CSF should be given from 24 hours after the last dose of cyclophosphamide until resolution of neutropenia in accordance with ASCO guidelines or institutional practice. Long-acting (pegylated) G-CSF may be substituted according to institutional practice as described in Section 8.7.1
17. Core needle biopsies for research are required at baseline, Week 8, and at progression, with the exception of subjects for whom there is no safely accessible tumor tissue. Archival tissue may be used for screening. The baseline biopsy should be collected as close to the start of lymphodepleting chemotherapy as possible, but no more than two months prior. Exosome/ ctDNA samples should match biopsy time points.
18. If pharmacogenetics sample collection is not done at baseline, it may be done at any other subsequent visit while the subject is in the interventional phase of the study. Collection of a pharmacogenetics sample is optional and all subjects who participate must provide consent for pharmacogenetics blood sample collection.
19. Pre-infusion, Week 3, Week 8, and Week 12 blood collection is for both Cytokine and Immunogenicity responses and is collected in one 3 mL tube. If CRS is suspected, cytokines should be collected every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.
20. Vector copies for safety samples are collected Day 1 (pre-infusion) and then every 6 months post-infusion up to 5 years (Section 10.3.4 for more details). For RCL, samples are collected Day 1 (pre-infusion), and at Week 12, Week 24, and 1 year post-infusion and then annually for up to 15 years.
21. ECG on the day of T-cell Infusion (Day 1) may be performed at any time pre-infusion. ECG can also be performed at other time points if medically indicated. Triplicate ECG will be collected at Treatment Eligibility Screening / Baseline visit and single ECGs at other timepoints. Participants with clinically significant cardiovascular risk factors (as per Section 7.4.8) will undergo evaluation by a cardiologist prior to lymphodepletion.
22. 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.
23. Revised lymphodepletion schedule only given if cohort expands and lymphodepletion regimen changes.

24. 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 known 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 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.
25. Samples for TCR antibodies are to be taken on the day of T-cell infusion (Day 1), at Weeks 3, 5, 8, 12, and 24, at Months 9, 12, 18 and 24, and at study completion or withdrawal.

Table 5 Schedule of Procedures in Long-Term Follow-up Phase prior to Transfer to LTFU Study 208750

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 months									± 6 months
Safety Assessments												
Medical History and Physical Exam1	X	X	X	X	X	X	X	X	X	X	X	X
Mutagenic agents, other investigational agents or anti-cancer therapies1	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events and Serious Adverse Events2	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X		X		X		X		X	X3
Serum chemistry	X	X	X		X		X		X		X	X3
Pregnancy Test (for WOCBP)4	<==========X4==========											>
Central Lab												
VSV-G DNA (RCL) for safety5	X	X	X		X		X		X		X	X
Vector Copies (Persistence) for safety6	X	X	X	X	X	X	X	X	X	X	X	X3
Other Assessments												
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X

1. New medical history/medications/chemotherapies.
2. Adverse event collection is limited to:
   - New malignancies
   - New incidence or exacerbation of a pre-existing neurologic disorder
   - 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 and/or hospitalization deemed related to gene modified cell therapy

3. In year 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 10.3.3 and Section 10.3.4) then laboratory assessments are discontinued.
4. For WOCBP, pregnancy testing should be conducted during contraception period only as defined in Section 4.1, Inclusion Criteria. When pregnancy testing is performed at visits where hematology sample is collected, blood pregnancy testing will be done. At visits where hematology testing is not performed, urine pregnancy test is acceptable unless serum testing is required by local regulation or IRB/IEC.
5. Samples for RCL (VSV-G copies) are collected as described in Section 10.3.1.
6. Samples for persistence are collected as described in Section 10.3.3, and Section 10.3.4.

7.4. Clinical Assessments and Procedures

7.4.1. Demographics

Demographic data including age, gender, race and ethnicity will be collected at screening.

7.4.2. Disease History

The following information will be recorded in the eCRF for myxoid/ round cell liposarcoma: primary tumor type, date of initial diagnosis, location of disease at initial diagnosis, stage at initial diagnosis, type of histology, histological grade, results of any historical molecular testing performed (if available), date of diagnosis of metastatic disease, location of disease, stage at screening.

7.4.3. Medical History

Relevant medical history will be recorded at screening in the subject's medical record and eCRF.

7.4.4. Physical Examination and Vital Signs

At baseline, subjects will undergo a physical examination including weight, height and measurement of vital signs (temperature, heart rate, respiratory rate, and blood pressure). The frequency of physical examination, weight and vital signs assessments at subsequent visits is specified in the Schedule of Procedures (Table 4).

7.4.5. Performance Status

At baseline, performance status will be measured using the ECOG performance scale (see Section 16.2). It is recommended, where possible, that a subject's ECOG be assessed by the same person throughout the study. The frequency of the ECOG assessment is specified in the Schedule of Procedures (see Section 7.3).

7.4.6. Clinical Safety Assessments

Subjects will be assessed for AEs throughout the study. Specific grading systems for Cytokine Release Syndrome (CRS) and Graft versus Host Disease (GvHD) are described in Section 8.5 and Section 8.6 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.

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

7.4.7. Laboratory Assessments

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

The following assessments will be conducted in order to monitor subject safety. Refer to Section 16.3 for listing of lab tests

- Hematology
- Biochemistry
- Coagulation
- C-reactive Protein
- CMV viremia (see Section 8.2.1)
- Urinalysis

Female subjects of childbearing potential (WOCBP must have a negative pregnancy test at screening, within 24 hours prior to starting lymphodepleting chemotherapy, and monthly thereafter during the interventional phase of the study as indicated in Section 7.3.

Please refer to Schedule of Procedures for additional information regarding the frequency of these assessments.

7.4.8. Cardiac Assessments

All cardiac assessments will be performed locally at the site.

The following assessments will be conducted in order to monitor subject safety:

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

- ECGs: refer to Section 16.3 for the ECG parameters required

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

For subjects with cardiac or pericardial disease at baseline, inpatient telemetry monitoring will be carried out for a minimum of three and up to seven days post [TCR] infusion.

Participants with clinically significant cardiovascular risk factors such as but not limited to:

  - prior cardiac insult (ie, prior myocardial infarct and prior coronary revascularization)
  - significant valvular disease
  - low ejection fraction

- cardiomyopathy
- history of heart failure
- significant cardiac arrhythmias
- history of cardiac toxicity from prior therapies
- baseline tumor masses in close proximity to the cardiac muscle

must

- undergo evaluation by a cardiologist prior to lymphodepletion
- be monitored by inpatient continuous cardiac telemetry for a minimum of 3 days post T-cell infusion and as long as deemed necessary by the Investigator.

In these participants with clinically significant cardiovascular risk factors, all reports of cardiac events following treatment with NY-ESO-1^{c259}T infusion will continue to be monitored through normal proactive Pharmacovigilance to determine causality. Supportive care for these participants will be provided per standard clinical practice guidelines.

7.4.9. Pulmonary Assessments

Participants with known lung metastases (active or previously treated with surgical resection or radiotherapy) should be considered for pulmonary consultation prior to lymphodepletion, which may include pulmonary function tests.

Participants deemed at high risk for pulmonary complications per the pulmonologist should have closer post-infusion monitoring during the following periods:

- post T-cell infusion, for a minimum of 3 days and as long as deemed necessary by the Investigator
- if CRS is suspected, for the first week and until symptoms are improving or an alternative diagnosis is confirmed

and should include:

- Close monitoring of chest imaging, as clinically indicated
- Close monitoring of fluid balance
- Continuous cardiac telemetry monitoring.

Participants who have an airway that may be compromised should be assessed prior to lymphodepletion, including considerations such as speech and swallow evaluation, anaesthesia consultation, or consideration for closer post-infusion monitoring (as above) in the event their airway may be compromised due to tumor inflammation, prior surgery/radiation, decreased consciousness, infection or other cause.

7.4.10. 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.

Immune Effector Cell-Associated Encephalopathy (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. Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following NY-ESO-1^{c259}T infusion. If a subject 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.

7.4.11. Tumor Response Assessments

Tumor assessments for response and progression will be evaluated at Baseline (within 1 week prior to chemotherapy), Week 4, Week 8, Week 12, Week 24, and every 3 months until disease progression and again at study completion/withdrawal, according to the RECIST v 1.1 criteria (Section 16.4).

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 CT scan with oral and/or i.v. iodinated contrast of the chest and abdomen/pelvis (CT is the preferred modality for tumor assessments)
- MRI of the abdomen/pelvis acquired before and after gadolinium contrast agent administration and a non-contrast enhanced CT of the chest, if 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.

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. Prior to starting the study, a detailed imaging acquisition protocol (Site Imaging Manual) will be provided to the sites to describe the requirements for image acquisition and the standardized procedure for the transfer of image data to the central vendor.

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 (complete response [CR] or partial response

[PR]) should be confirmed by repeat imaging scan performed 4 weeks (but not earlier) after the criteria for response were first met.

Confirmatory scans should be completed in advance of the next scheduled visit if the next scan is due more than 4 weeks after the response is first observed.

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

A central vendor will collate study images. Review and interpretation of tumor response according to RECIST v1.1 will be conducted by an appropriately qualified, trained and experienced reviewer.

A written Site Imaging Manual will be provided to sites to describe the imaging acquisition protocol and standardized procedure for the transfer of image data to the central vendor. The 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. The study has the option to collect and hold scans for review at a later date rather than advancing to read and report upon receipt by the central vendor.

7.4.12. Long-Term Follow-up

All subjects will be followed for 15 years from time of T cell infusion for observation of delayed adverse events in accordance FDA and EMA requirements for gene therapy clinical trials. [FDA Guidance, 2006b; FDA Guidance, 2010; FDA Guidance, 2020].

Subjects will be seen and laboratory analysis conducted at 3, 6, and 12 months in the first year post-infusion. Subjects will be seen in the clinic and samples taken every 6 months in years 2 -5 and then annually from years 6-15. Assessments will include medical history, physical exam, and reporting of adverse events, plus exposure to mutagenic agents, anti-tumor agents and other medicinal products. Assessments will be collected under GSK208469 (ADP-0011-007) while subjects are on the interventional phase. After completion of the Study 208469 interventional phase, assessments may be collected either under the LTFU protocol GSK208750 (ADP-0000-002) or under the current protocol until the LTFU GSK208750 is available.

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

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 the outcome of the treatment, such as T Cell phenotype, function and persistence of the engineered infused cells as well as evaluate candidate biomarkers and correlate with clinical response to treatment. These

studies will be performed on tumor biopsies, serum/plasma and fractionated PBMC samples collected according to the schedule of procedures. All samples will be processed and/or frozen following trial specific SOPs and analyzed either by central laboratory facilities contracted by the Sponsor or by the Sponsor itself at the Sponsor's facilities. Documentation for sample receipt, processing and storage, and primary data from the research analyses will be collected and stored at the Central Lab or at GSK as appropriate.

Research studies conducted on blood samples may include, but are not limited to the following:

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

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

Biopsy research studies may include:

- DNA and RNA analysis including PCR and in-situ hybridization to measure infiltration of T cells
- Genomic sequencing to assess T cell clonality through TCR Vbeta and Valpha sequencing
- Tissue expression of the target antigen (NY-ESO-1 and LAGE-1a)
- Tissue analysis for immune cell infiltrate and functional biomarkers (by single or multiplexed IHC) and gene expression profile (including by Nanostring or next-gen sequencing of RNA)
- Tissue analysis to determine the evolution of the mutation profile of the tumor over the course of the therapy by DNA sequencing analysis
- As new technologies and data emerge, other assays relevant to the study objectives may be performed

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

7.5.1. Pharmacogenetics Sample

A whole blood sample for pharmacogenetic research may be obtained at any time throughout the study (refer to Table 4) in addition to any blood samples taken for the clinical study. The pharmacogenetic sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). 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 providing that the subject has given written informed consent for pharmacogenetics research.

The Pharmacogenetic sample may be used to investigate the association of candidate or genome-wide genetic variants with efficacy (ORR, DOR) and safety such as but not limited to Cytokine Release Syndrome frequency/severity/duration.

7.5.2. Cytokine and Soluble Factors Analysis

Serum is collected at baseline, and at each visit post infusion up to 8 weeks, to allow for measurement of cytokines in the blood. Serum is also collected from subjects with suspected cytokine release syndrome (CRS), samples being taken approximately every other day until symptoms are improving or an alternative diagnosis is confirmed. Details regarding serum collection are provided in the SPM.

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

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 as the presence of antibodies to NY -ESO-1^{c259}T.

7.5.3. Tumor Biopsies

The efficacy of immunotherapy of cancer is conditioned by the infiltration of tumors by activated tumor-specific T cells. The activity of these T cells will in turn be affected by the presence in the tumor of an immunosuppressive environment (e.g., regulatory T cells). Therefore, the direct evaluation of the "immune landscape" inside the tumor is of great value for understanding and optimizing cancer immunotherapy. For this reason, core needle biopsies are mandated 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 at the time of documented disease progression, with the exception of subjects for whom there is no safely accessible tumor tissue.

Archival tissue may be used for the screening biopsy, although fresh tissue is preferred. If fresh tissue is provided at screening, and sufficient material is available for research

studies, the baseline biopsy can be omitted. Otherwise the baseline biopsy material should be collected any time 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 and 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 noted at the time (e.g., decreased, stable, increased size or activity).

If feasible, biopsy material should be collected at the time of documented disease progression, ideally on lesions that have progressed.

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

In subjects who have effusions, should there be a clinical requirement for removal of the effusion fluid at any time during study, samples are requested to be collected for GSK for translational research studies. If available, effusion fluid should be collected in addition to and not instead of the requested tumor biopsies.

Clinically obtained effusion samples have been shown to be a rich source of tumor cells, tumor infiltrating leukocytes and soluble factors. Effusion fluid collected in this protocol will be used to interrogate soluble and cellular components of the tumor microenvironment before and after T cell infusion to address mechanisms of sensitivity or resistance to therapy.

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

The primary research assays for the trial involve monitoring for the persistence of infused engineered cells in the subjects and for correlation of this with potential therapeutic effect. Persistence is also monitored long term as a safety measure (Section 10.3.3). Two well established methodologies will be used to measure the cells; quantitative polymerase chain reaction (qPCR) and flow cytometry (FCM).

- Quantitation of NY-ESO-1^{c259}T TCR+ cells by PCR of transgene from DNA extracted from frozen PBMC. This will be used as a measure of pharmacokinetics.

- Quantitation of NY-ESO-1^{c259}T TCR expression cells by flow cytometry (FCM) from frozen PBMC

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

A range of assays will be performed to elucidate the phenotype and activity of the gene-modified T cells before (manufactured product) 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 (analysis may not be limited to these assays; additional assays may be added as they become available).

- Phenotype analysis for determination of T cell lineages in manufactured cell product prior to infusion and in the blood (and tumor if resection performed) post infusion over time

- 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}T 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

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 will be collected in parallel, covering complementary materials that might provide information about 1) the tumor microenvironment (inflammatory or immunosuppressive profile) and 2) the immune response mediated by the NY-ESO-1 TCR- transduced T cells. These materials are cell-free DNA (cfDNA) and exosomes (source of stable mRNA).

Exosomes (produced by all cells, including tumor cells and immune cells) and cfDNA (produced by dying tumor cells) will be used to monitor both the molecular signature of the tumor burden and the immune response. The analysis of exosomes and cfDNA will allow:

- Estimation of the global tumor mutational burden and genomic profiling from cfDNA.

- RNA expression profiles including expression of NY-ESO-1 and LAGE-1a mRNA from exosomes.

- 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 EMEA guidance [FDA, 2006a; EMEA, 2009] all subjects who are enrolled in this trial are asked to consent to autopsy and autopsies 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 SPM.

7.6. Retreatment

Subjects who achieved a confirmed CR or PR or SD ≥3 months following first GSK3377794 infusion will have an option to receive a second course of conditioning chemotherapy and GSK3377794 under the following conditions:

- Subject had a confirmed CR or PR or SD ≥3 months following first GSK3377794 infusion
- Subject's disease subsequently progressed in >3 months after first infusion
- Eligibility based on NY-ESO-1 expression from fresh biopsy is confirmed (from 1st infusion progression biopsy optimally obtained prior to receipt of any additional systemic anti-cancer therapy). In cases where second lete-cel infusion is permitted after patients have received subsequent anti-cancer therapies post-progression from first lete-cel infusion, a recent biopsy sample collected after progression from recent anti-cancer therapy should be confirmed for NY-ESO-1 expression. If acquisition of a post-progression biopsy sample is not feasible, alternatives may be discussed with the medical monitor.
- Subject continues to meet the original study eligibility criteria with the exception of
    - Exclusion criterion 1: prior GSK3377794 use in this study as defined in Section 4 and per Section 7.6.1. and
    - Inclusion criterion 12: Subject is fit for apheresis and has adequate venous access for the cell collection
- Screening assessments must be repeated if clinically indicated, as determined by the investigator, to confirm eligibility
- Subject has not received systemic anti-cancer therapy for the treatment of sarcoma with the exception of bridging therapy which is permitted. If subjects have received subsequent anti-cancer therapies post-progression from first lete-cel infusion, administration of second lete-cel infusion may be permissible on a case-by-case basis upon discussion with the medical monitor.
- Subject did not experience a Grade 4 CRS event or Grade 4 neurologic toxicity after the first GSK3377794 infusion
- Toxicities related to conditioning chemotherapy with the exception of alopecia, have resolved to ≤Grade 1 or returned to baseline prior to retreatment
- Sufficient cell dose is available from the original manufacturing procedure to allow for retreatment (i.e. subjects will not undergo repeat leukapheresis) and within shelf-life specifications. No new leukapheresis or manufacture will be performed.

The decision to administer retreatment must be made in consultation with the medical monitor. In addition, a discussion regarding benefits and risks of retreatment should occur

with the subject prior to performing any study-related procedures or treatment. This conversation should also be recorded in the subject's source document.

Subjects must be reconsented prior to performing any study related procedures or treatment.

A maximum of 1 retreatment course may occur per subject. Subjects who are retreated must follow the same treatment schedule and procedural requirement per the initial retreatment. Data will be captured in the retreatment eCRF.

7.6.1. Benefit:Risk Assessment

See Section 3.5.

Allowance for retreatment is based on clinical experience across multiple studies of CAR and TCRs and prior experience from the lete-cel program. In 2 studies conducted at the pediatric [Lee, 2015] and Surgery Branch [Kochenderfer, 2015] of the National Cancer Institute (NCI) 6 subjects were re-treated upon progression. Three of the re-treated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression. Gauthier et al, [Gauthier, 2021] demonstrated that second infusions of CAR-T therapy were both feasible and induced responses in 39% of subjects, including CRs in 20%. Evidence of tumor regression post disease progression following a second infusion of TILs was demonstrated by Tran el al, [Tran, 2014] in a subject with cholangiocarcinoma. Similarly Hegde et al [Hegde, 2020] reported a second remission (CR) in a child with rhabdomyosarcoma following retreatment with HER2 CAR T cells following progression 6 months post first CAR T infusion.

In sponsored trials, a total of sixteen (16) subjects [11 subjects in Study 208466 (MRCLS) (formerly ADP-04511), 4 subjects in Study 209393 (multiple myeloma) (formerly ADP-01411), and 1 subject in Study 208749 (NSCLC) have received a second infusion of GSK3377794 after progressive disease following response (or prolonged stable disease) to their initial infusion. There were no fatal SAEs reported among subjects who received a second infusion of GSK3377794. Although the data is limited, the safety profile following a second infusion of GSK3377794 is consistent with that of all subjects infused.

In Study 208466, many of the subjects who underwent initial treatment with GSK3377794 demonstrated clinical benefit, with measurable tumor regression by RECIST 1.1 and investigator assessment observed in one third (33%) of subjects. On retreatment, 1 CR, 1 PR, and multiple SD were observed. In Study 208749 1 subject received a second infusion post progression and achieved SD.

Data from preclinical studies support the efficacy, specificity, and safety of GSK3377794 (Investigator Brochure). Clinical data from subjects who have undergone a second infusion demonstrate the safety and activity sufficiently to support retreatment.

7.6.2. Lymphodepletion and T-Cell Infusion

Lymphodepletion and T-cell infusion follow the same procedures as outlined in Section 3.2 and in Section 5.2 and Section 5.3.

7.6.3. Study Procedures

All study procedures should be carried out as defined for initial treatment, including safety and response assessment, with the exception of leukapheresis which is not part of retreatment or second treatment. See Section 7, Table 4. Assessments will follow the same schedule as for the first infusion.

7.6.4. Completion of Retreatment / Second Treatment Interventional Phase

Per Section 4.3, a GSK3377794 infused subject will be considered to have completed the interventional phase of the study when he/she has progression of disease (see Section 7.4.11 for tumor response assessments), death, or has been followed-up for 2 years after GSK3377794 infusion, whichever is shorter.

Subjects being considered for retreatment will enter the retreatment interventional phase on completion of the interventional phase.

Subjects who meet eligibility for and undergo retreatment will be considered to have completed the retreatment interventional phase of the study when they have progression of disease following retreatment, death, or have been followed-up for 2 years after re-treatment, whichever is shorter. The sponsor may terminate the study before all retreated subjects have completed the retreatment interventional phase. In such cases, these ongoing subjects will transfer to long term follow-up at that time.

All subjects alive on completing or withdrawing from the retreatment interventional phase will continue into long-term follow-up (LTFU) for observation of delayed adverse events as described in Section 7.4.12. If necessary and upon discussion with the Sponsor, those subjects who have not progressed after 2 years post retreatment and who are continuing in Study 208469 may continue to undergo response assessments every 3 months as defined in Study 208469 per institutional standard of care.

7.6.5. Long-Term Follow-Up

See Section 4.3.1 for details of long-term follow-up. For subjects who undergo retreatment, timing starts from second infusion of GSK3377794.

7.6.6. Response Assessment

Response assessment will be followed as per Section 7, Table 4. Assessments will follow the same schedule as for the first infusion.

If the subject is eligible for retreatment with GSK3377794, the last scans prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment as long as those scans are within 7 days prior to lymphodepletion for retreatment. If not within 7 days, baseline scans will be repeated prior to infusion.

7.6.7. Objectives

The following exploratory objectives will be investigated.

CCI

7.6.8. Statistical Methods

AEs associated with the first or the second infusion will be reported separately. Details will be described in the RAP.

Efficacy associated with the first or second infusion will be reported separately. Details will be described in the RAP.

7.6.9. Retreatment Study Populations

mITT2 Retreatment Analysis Set

The mITT2 retreatment analysis set will consist of all subjects who undergo retreatment with any dose of GSK3377794. This set will be used for all retreatment efficacy analyses.

Safety Retreatment Analysis Set

The safety retreatment analysis set will consist of all subjects who undergo retreatment with GSK3377794.

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 in the management of associated toxicities (e.g., cytopenias, cytokine release syndrome, 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.

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

Subjects should receive prophylaxis against Pneumocystis pneumonia, herpes simplex, and varicella zoster as per institution guidelines. In addition, measures to treat and prevent infection may be provided in accordance with institution guidelines. In particular, fever and neutropenia should be aggressively managed as well as pre-emptive influenza therapy and other standard therapies for immunocompromised hosts. For participants with indwelling central lines, consider increased surveillance to monitor for catheter-associated infections.

8.2.1. Pneumocystis Carinii Pneumonia

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

8.2.2. Herpes Simplex and Varicella-Zoster

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

8.2.3. Cytomegalovirus

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. CMV seropositive subjects will be monitored for CMV viremia by CMV DNA PCR as shown in Table 4 until 60 days post infusion of NY ESO 1^{c259}T. In the event CMV viremia is

observed a specialist in infectious disease should be consulted and treatment initiated if necessary according to institutional practice.

If a subject experiences prolonged or recurrent 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 8.7.2.

8.2.4. Hepatitis B Prophylaxis

Subjects will be screened for hepatitis B (HBV) at study entry. Subjects who are hepatitis B core antibody positive must receive prophylaxis against viral reactivation using institutional protocols. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months.

8.2.5. Treponema

Subjects will be screened for treponema (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 lymphodepletion chemotherapy.

8.2.6. Other Anti-Microbial Prophylaxis

Antibacterial and antifungal prophylaxis should follow institutional standards for autologous bone marrow transplants. If a participant requires anti-microbial treatment associated with risk of cardiac toxicity, consider close monitoring of cardiac function (Section 7.4.8).

8.3. Hematologic and Blood Product Support

Blood product support should be provided to maintain:

- platelets >10 x10^9/L in the in-patient setting and platelets >20 x10^9/L in the out-patient setting
- Hb >8.0 g/dL

  or as clinically indicated in the judgement of the Investigator (in accordance with institutional practice).

  See AABB Guideline on platelet transfusion [Kaufman, 2015].

8.3.1. Blood Product Irradiation

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 study T cell infusion or until lymphocyte count returns to ≥1.0 $x10^9$/L (whichever is longer) must be irradiated. In addition, if a subject requires systemic steroids or immunosuppression for the treatment of toxicity, irradiated blood products must be given until recovery of immune function.

8.3.2. CMV Screened Blood Products

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

8.4. Management of Autoimmunity

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

8.5. Management of Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a potentially life-threatening toxicity that has been observed following administration of antibodies and adoptive T-cell therapies for cancer. It is defined clinically by symptoms many of which mimic infection including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash and dyspnea. It is important to evaluate the subject for concurrent infections. Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure and disseminated intravascular coagulation. CRS may also be associated with findings of macrophage activation syndrome or occur coincident with tumor lysis syndrome.

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

Table 6 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be

implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical, and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels as described in Section 7.5.2 as well as 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[1,2]	Management Guidelines
1	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.	Vigilant supportive care[4] Assess for infection and treat[5]
2		Monitor cardiac and other organ function Vigilant supportive care[4] Assess for infection and treat[5] Treat hypotension with fluid and pressors Administer O2 for hypoxia[6] Consider administering tocilizumab ± corticosteroids[7]
3		Monitor participant very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). Vigilant supportive care[4] Assess for infection and treat[5] Treat hypotension with fluid and pressors[6]. Administer O2 for hypoxia. Administer tocilizumab ± corticosteroids[7]
4		Manage participant in ICU Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required[6] Administer tocilizumab ± corticosteroids[7]
5		

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.

CCI [redacted]
CCI [redacted]

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 CCI [redacted] CCI [redacted]. 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 CCI [redacted] CCI [redacted] CCI [redacted]

Grade 3 CRS is defined as CCI [redacted] 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.

Grade 4 CRS is defined as CCI [redacted] 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. [redacted] CCI [redacted] 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 CCI [redacted] 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, 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., recommend administration of tocilizumab 4 mg/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, 2014 and 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 adoptive T-cell therapy. 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 cytokine release syndrome is suspected, a physician with expertise in the management of subjects following bone marrow transplantation 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.

If CRS is suspected, participants deemed to have significant cardiovascular risk factors (per Section 7.4.8) should be considered for earlier intervention with tocilizumab and/or steroids at the onset of CRS.

If CRS ≥ Grade 2 is suspected, an ECHO/MUGA is required at onset of ≥ Grade 2 CRS. Additional monitoring must be conducted for a minimum of 3 days post onset of ≥ Grade 2 CRS and as long as deemed necessary by the Investigator:

- Continuous cardiac telemetry monitoring
- ECHO/MUGA as clinically indicated
- Local tests:
  - Daily troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) or BNP tests.

If, in the opinion of the Investigator, a participant develops any clinically significant new or worsening cardiovascular symptoms or abnormal cardiac labs / imaging finding, a cardiology consult should be conducted for urgent evaluation.

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

Autologous graft-versus-host disease (GvHD) has been described in association with adoptive transfer of ex-vivo expanded/co-stimulated autologous T cells [Rapoport, 2009],

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

8.6.1. Diagnosis of GvHD

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

Organ	Findings/Symptoms	Differential Diagnosis	Histopathology
Skin	Maculopapular rash involving the neck and shoulders as well as the palms and soles that spreads to include the rest of the body.	Drug reactions, viral exanthems, cytokine release syndrome, and effects of chemotherapy or radiation	Apoptosis at base of epidermal rete pegs, dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes and perivascular lymphocytic infiltration in the dermis.
GI	Secretory diarrhea is most common but nausea, vomiting, anorexia, weight loss and abdominal pain can also occur. Diarrhea can be copious. Bleeding may result from mucosal ulceration and ileus may ensue.	Side effects of chemotherapy or other drugs and infection of the GI tract	Patchy ulcerations, apoptotic bodies at crypt bases, crypt ulceration and flattening of surface epithelium

Organ	Findings/Symptoms	Differential Diagnosis	Histopathology
Liver	Cholestatic pattern of liver injury including elevated conjugated bilirubin, alkaline phosphatase and GGTP. Subjects may present with jaundice, with pruritis in more severe cases.	Veno-occlusive disease of the liver, viral infections, drug toxicity and sepsis.	Endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis and bile-duct destruction.

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.

8.6.2. Grading of GvHD

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

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.

With the addition of assessment of functional impairment, grading can be determined using the table below [Glucksberg, 1974].

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8.6.3. Management of GvHD

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

If GvHD is suspected:

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

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

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

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

Grade	Management Strategy
I	Subjects with grade I disease are not likely to require systemic treatment. Cutaneous GvHD may respond to topical steroid creams. Antihistamines may be helpful in subjects with 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.

Grade	Management Strategy
III	For more severe or progressive symptoms consider systemic corticosteroids (e.g., methylprednisolone one (1) mg/kg per day*)
IV	Methylprednisolone two (2) mg/kg per day*
* The use of 'nonabsorbable' steroids (Budesonide and beclomethasone) can be considered for acute intestinal GvHD in order to reduce the dose of systemic steroids	

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

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

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

Most allogeneic transplant subjects concurrently receive 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 Hematology and the British Society for Blood and Marrow Transplantation guideline for diagnosis and management of acute graft- versus-host disease [Dignan, 2012].

8.7. Chemotherapy Symptom Management

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

8.7.1. Management of Neutropenia

The pre-conditioning chemotherapy is intended to cause lymphodepletion, however, neutropenia is also common. Prophylactic use of G-CSF (e.g., filgrastim) should be used in all subjects for the management of neutropenia according to ASCO guidelines. G-CSF should be given starting 24 hours after the administration of chemotherapy and continued until reaching an absolute neutrophil count (ANC) of at least 2 to 3 $x10^9$/L.

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.

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

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

- Absolute neutrophil count ≥ 1 x10^9/L for 2 consecutive measurements approximately 7 days apart, and
- Platelet count ≥ 20 x10^9/L without transfusion support for one week.

Aplastic anemia is a rare hematological disorder characterized by pancytopenia and a hypocellular marrow. Patients are usually symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. The diagnosis of severe aplastic anemia is made in the setting of a hypocellular bone marrow when 2 of the following 3 blood counts are met: absolute neutrophil count < 0.5 x10^9/L, absolute reticulocyte count < 60 x10^9/L, and platelet count < 20 x10^9/L, 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. Please refer to Section 7.5 (Correlative Studies and Research Assessments). Details on tissue collections, kit use and shipment information can be found in the SPM.
- A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the Sponsor. Please refer to Section 8.6 (Management of Graft- versus-Host Disease) regarding bone marrow suppression as a feature of GvHD.

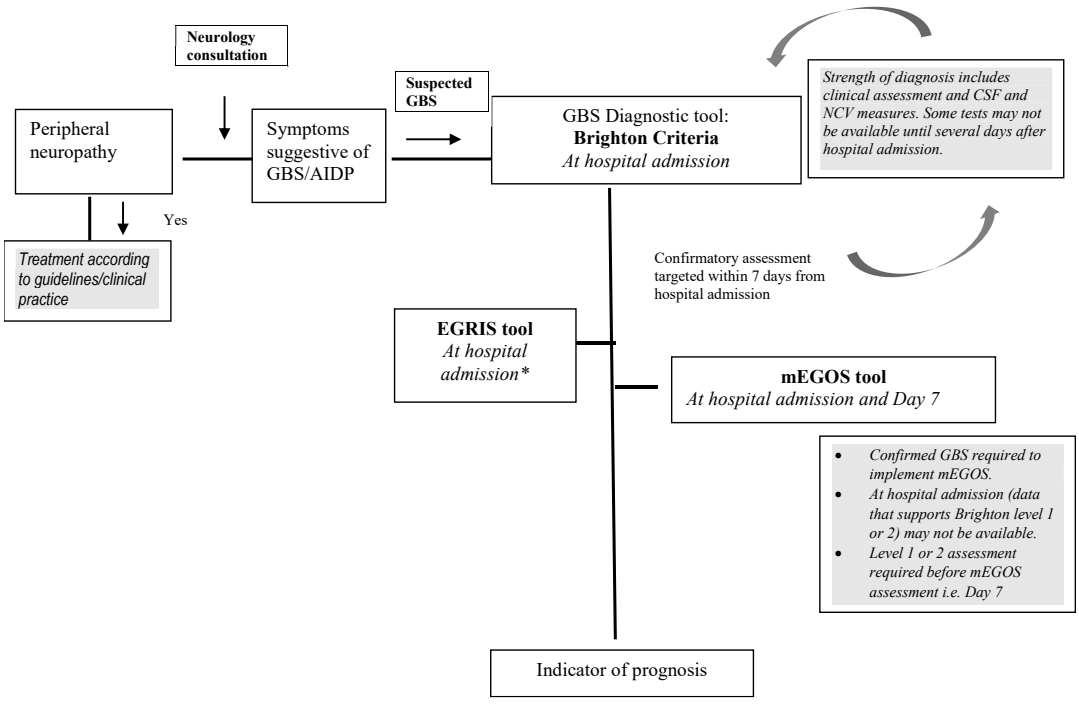
- Initiate treatment with G-CSF
- Consult an Infectious Diseases expert
- Once alternative etiologies have been excluded, strongly consider immunosuppression (e.g., methylprednisolone 2mg/kg initial dose) or more aggressive regimens (e.g., antithymocyte globulin (ATG), cyclosporine, eltrombopag) as well 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 8.6.3 (Management of Graft-versus-Host Disease) regarding bone marrow suppression as a feature of GvHD.

8.7.3. 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.

Figure 2 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 3.

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

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

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

Modified Erasmus GBS Outcomes Score (mEGOS)

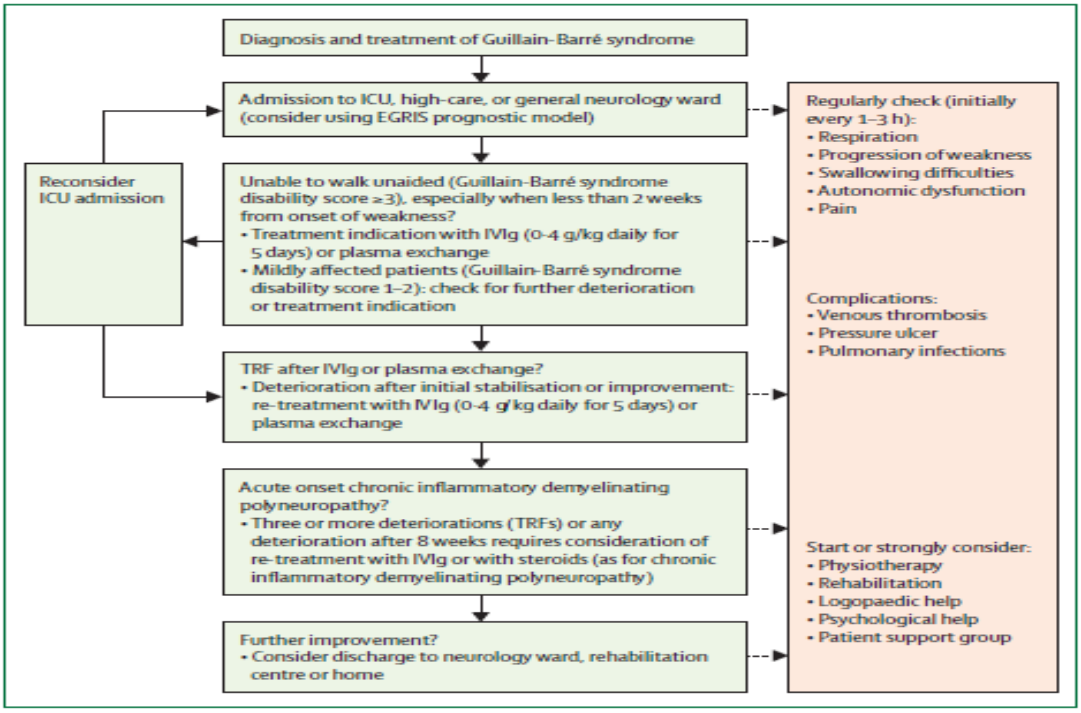
Parameters required at hospital admission and 7 days later [Walgaard, 2011]:

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

8.7.3.1. Summary of diagnosis and treatment for GBS

Additional information on the diagnosis and management of GBS (Figure 1) can be found in a review article on GBS [Willison, 2016].

Figure 3 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 (or designee) is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. Individual AEs should be evaluated by the investigator and should be

reported to the Sponsor as appropriate. This includes the evaluation of its intensity, the causality between the investigational medicinal product and/or concomitant therapy and the adverse event 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 Section 7.3 (Schedule of Procedures).

- Any SAE, any AE related to study procedure or AE leading to withdrawal from the study will be collected from signature of the subject Screening ICF.
- All AEs and SAEs will be collected and reported from the time of leukapheresis until the subject has completed or withdrawn from the interventional phase of the study. All SAEs must be collected through 90 days following T cell infusion, or 30 days following T cell infusion if the participant initiates new anticancer therapy, whichever is earlier.
- All SAEs have to be reported to sponsor within 24 h of Investigator learning about them.
- During LTFU (15 years post infusion), subjects will only be monitored for those emerging clinical conditions defined in Section 9.4.

All AEs should be followed until:

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

9.2. Definition of Adverse Event

In accordance with the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a subject or clinical investigation subject who receives a pharmaceutical product. The event does not necessarily have a causal relationship with study treatment to be an AE. An AE can therefore be 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 of laboratory test abnormalities as AE, refer to Section 9.9.

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

9.2.1. Assessment of Intensity

Adverse events will be graded according to the NCI Common Toxicity Criteria for Adverse Events (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 7:

Table 7 Grading of AEs not specified in CTCAE v4.0

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9.2.2. Assessment of Causality

The investigator will assess the causal relationship between the adverse event and investigational 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 SAE eCRF accordingly. The investigator causality assessment is one of the criteria GSK use to determine regulatory reporting requirements for an SAE.

9.3. Reporting Serious Adverse Events (SAEs)

An SAE is any adverse event that:

- Is fatal (results in death; death is the outcome, not the event).

- Is life-threatening (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 in-subject hospitalization or prolongation of existing hospitalization.

- Results in a persistent or significant incapacity or substantial disability.

- Is a congenital anomaly/birth defect.

- Is medically significant or requires intervention to prevent one or the outcomes listed above.

Medical and scientific judgment should be exercised in deciding if an adverse event 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 inpatient 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 inflammatory demyelinating polyneuropathy must be reported as an SAE within 24 hours.
- Neutropenia grade 4 lasting ≥28 days

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 the electronic data capture (EDC) system. In addition, an SAE Worksheet must be completed and submitted to GSK within 24 hours by e-mail to OAX37649@GSK.com and RD_NYESOSAE@gsk.com (or fax: +44 (0) 20 8754 7822). The SAE eCRF must be completed by the investigator with as much information as is available. The minimum reporting criteria for an SAE include:

- Identifiable subject (Subject ID)
- Serious Adverse Event
- Suspect medicinal product
- Relationship to investigational product
- Identifiable reporting source (PI acknowledgment of the report and his/her signature is required)

The investigator will assess the causal relationship between the SAE and investigational product according to his/her best clinical judgement. The investigator will also assess the causal relationship between the SAE and the lymphodepleting chemotherapy. Further details can be found in the SPM.

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 according to FDA and EMA guidance [FDA, 2006b; EMEA, 2009; FDA, 2020]. Subjects will be followed according to the schedule outlined in Table 4. 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 pre-existing neurological 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 or hospitalization deemed related to gene modified cell therapy

A detailed narrative description of the event should include the date of diagnosis and the nature of the diagnosis for all AEs. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites. If a new malignancy is recorded in a vector target cell type, tumor cells will be evaluated for vector sequences. If the tumor is positive for vector sequences or the surrogate sample is positive for vector sequences and is confirmed in accordance to this protocol, clonality analysis will be performed. If no evidence of oligo- or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled, and submitted within the annual report of the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. Adverse events should be recorded in the eCRF using a diagnosis or possible diagnosis, and rated for intensity, causality and seriousness. If photographs are requested by the Sponsor of e.g., a rash AE, the subject will sign a Medical Photograph Release prior to any photographs being taken. 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 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 is 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 disease 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/ Research Committees (RC) and other study participants. GSK will comply with all GCP and country specific regulatory requirements relating to safety reporting to the regulatory authorities, IRBs/RCs and investigators.

Investigator safety reports for suspected unexpected serious adverse reactions (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/RC if appropriate, in accordance with local requirements.

On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor will submit detailed records of all adverse events 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 including those attributed to progression of malignant disease, 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 CV (including sudden cardiac death) and non-CV death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (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.

9.7.1. 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. 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 CAR-T 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 ACT of TCR T cells. 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 CNS tumors. 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.

9.8.1. Grading of ICANS

[Lee, 2019] have developed a new grading system for ICANS which incorporates the use of a modified version of the CARTOX 10-point neurological assessment tool termed Immune Effector Cell-Associated Encephalopathy (ICE) Points are assigned for each of the tasks which are performed correctly. Normal cognitive function is defined by an overall score of 10. The ICE should be used to monitor all participants ≥12 years old for ICANS.

Table 8 Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool

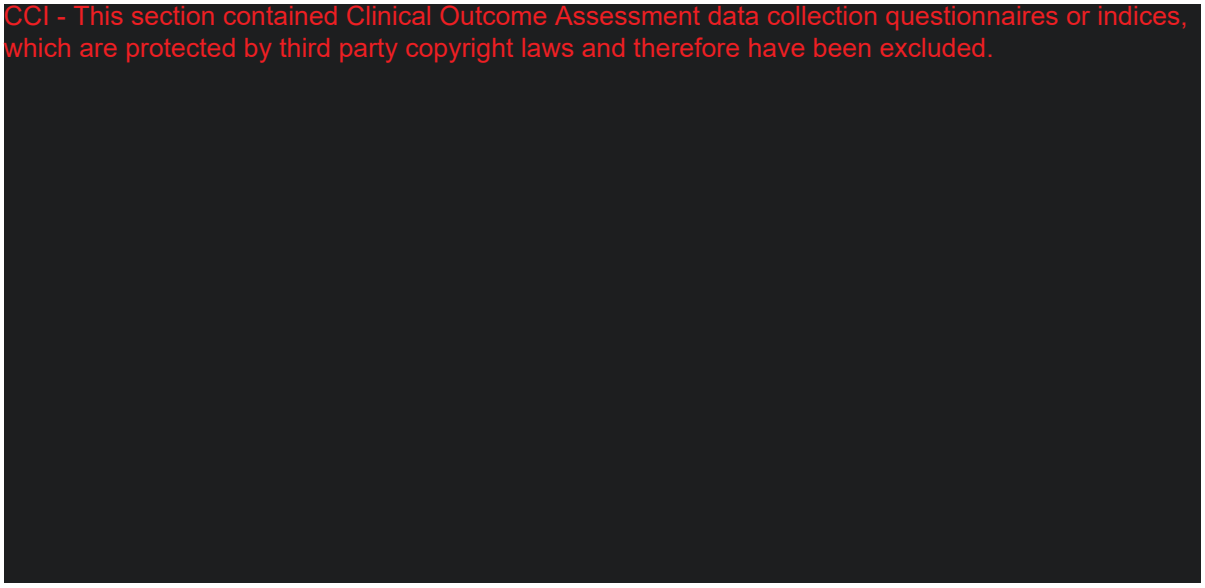
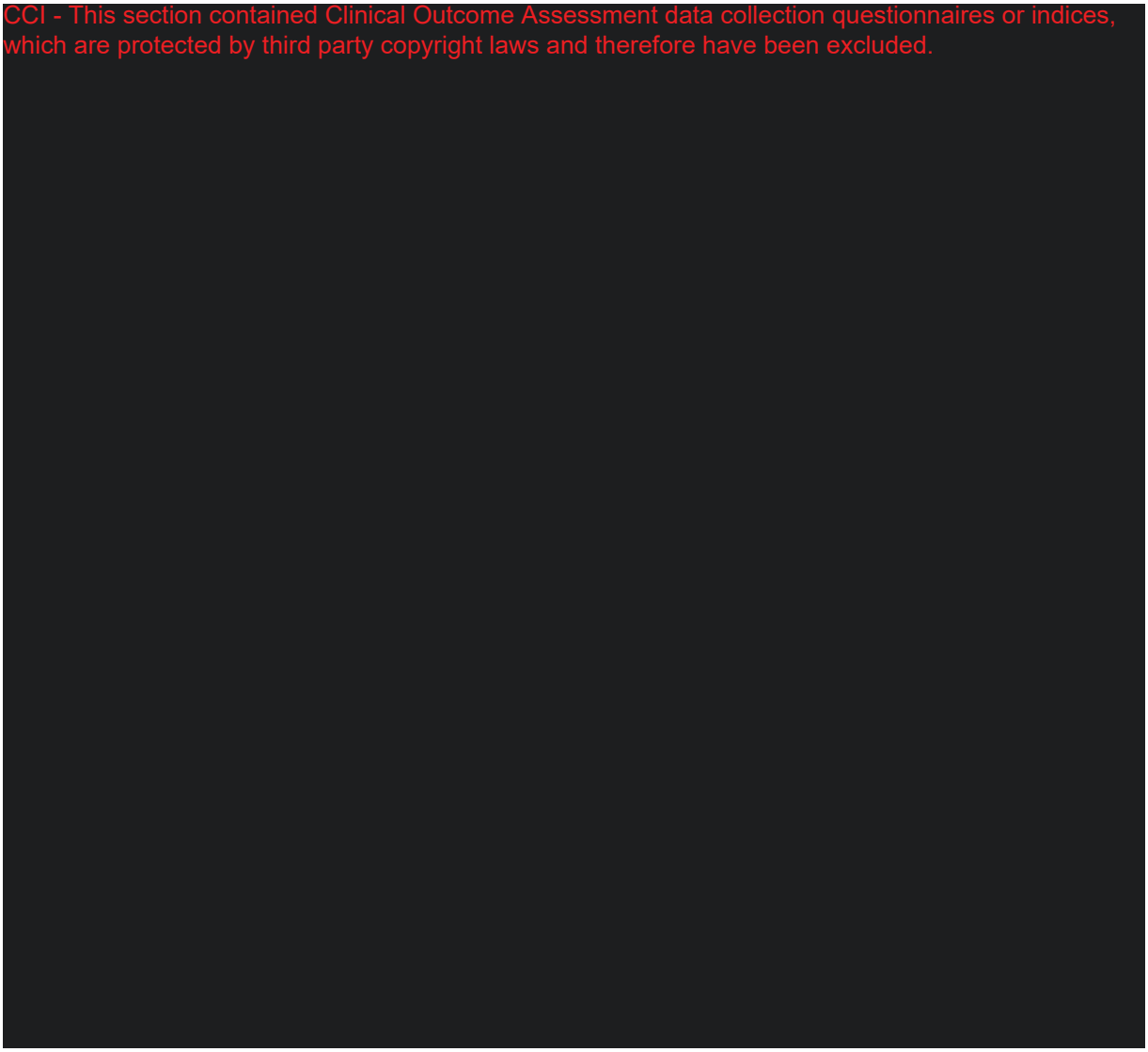


Table 9 Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

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.



9.8.2. Management of ICANS

The recommended management of ICANS should be based on toxicity grade. Table 10 provides guidance on the management of ICANS, and should be implemented in accordance with institutional guidelines.

Grade 1 ICANS is primarily managed with supportive care as outlined below. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be the first line treatment 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 EEG and neuroimaging as indicated.

Table 10 Management of ICANS

Grade	Treatment
1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired • Avoid medications that cause 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] IV or siltuximab 11 mg/kg IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent CRS
2	• Supportive care and neurological work-up as described for grade 1 ICANS • Anti-IL-6 therapy if associated with concurrent CRS • 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 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 ES and then taper • Stage 1 or 2 papilloedema with 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

Abbreviations: CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome; ICU = intensive care unit; IL-6 = interleukin-6; IV = intravenous; MRI = magnetic resonance imaging.
1. Maximum amount of tocilizumab per dose is 800mg.

Grade 1 ICANS. CCI

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.

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.

Grade 2 ICANS. CCI
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.

Grade 3 ICANS. CCI
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.

Grade 4 ICANS. CCI
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.

Grade 5 ICANS. CCI
CCI

9.9. Pregnancy

There is no preclinical or clinical trial data of NY-ESO-1^{c259}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 starting at the first dose of chemotherapy and for at least 12 months after

receiving the investigational product, or four months after there is no evidence of persistence/gene modified cells in the 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 study drug. However, the investigator shall report all pregnancies immediately to the Sponsor. A woman who becomes and remains pregnant during the study will be discontinued from the interventional phase as exposure to radiation from imaging studies would be contraindicated in this setting. The subject would enter into the LTFU protocol GSK208750 (ADP-0000-002). The outcome of the pregnancy must also be reported to the Sponsor. The contraception guidelines in the inclusion criteria of this protocol should continue to be followed during the LTFU.

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

9.10. Preexisting Condition

A preexisting condition is one that is present at the start of the study and must be recorded in the subject's Medical History. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

9.11. Laboratory Test Abnormalities as Adverse Events

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

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

Table 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	"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

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
	event or death is reported			
Pregnancy	24 Hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up 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 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 enrolment 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.

10.1.1. Mandated Study Pause Due to GBS

The occurrence of any event of GBS will mandate a pause in enrolment and stopping treatment for all participant within the GSK3377794 studies.

10.2. Stopping Rules

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

- Any death occurs that is deemed to be probably or definitely related to the investigational medication/cell product by the principal investigator and study sponsor;

  Or

- Two (2) or more grade 4 autoimmune events deemed probably or definitely related to the investigational medication/cell product by the principal investigator and study sponsor;

- Any event of Guillain-Barre syndrome (GBS) as diagnosed by a neurologist according to diagnostic guidance for GBS [Fokke, 2014].

  Or

- An apheresis confirmed positive biological replication competent lentivirus (RCL) occurs (see Section 10.3.2).

Following assessment by Sponsor, enrolment and dosing may resume if agreed upon by the Sponsor and regulatory authorities, if applicable.

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 Guidance, 2006b; EMEA Guideline, 2009].

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

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject [FDA Guidance, 2006b; EMEA Guideline, 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 until an understanding of how to manage the subject becomes clear.

Approaches that have been discussed for managing the subject are the following:

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

10.3.1. Testing for RCL in clinical studies

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

1. The cell product will be tested by or under the direction of the facility responsible for the manufacturing and release of the vector
2. Subject PBMCs which will be collected prior to infusion of transduced T cells and then at 3, 6, and 12 months post treatment. If vector persistence is undetected for two consecutive visit assessments and the participant is ≥2 years post-infusion, samples for RCL and persistence of gene modified cells will be discontinued. If VSV-G DNA copies are detected at any time point in the first year post-infusion, the safety monitoring protocol (Section 10.3.2) will be triggered and 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 biorepository.

10.3.2. Safety Monitoring - Results

If a positive VSV-G DNA signal is obtained, the study 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 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 test will be performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product [Manilla, 2005].

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

10.3.3. Persistence and Insertional Oncogenesis Testing and Monitoring

Monitoring for insertional oncogenesis follows the recommendations described in FDA and EMA guidance [FDA Guidance, 2006b; EMEA Guideline, 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 resulting 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]. Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMEA guidances [FDA, 2006a; FDA, 2006b; EMEA Guideline, 2009].

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

Peripheral blood mononuclear cells (PBMCs) samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects at 3, 6, 9 and 12 months post-infusion, then every 6 months until 5 years post-infusion and every year from year 6 post infusion in accordance with the FDA and EMA guidance [FDA, 2006a; FDA, 2006b; EMEA Guideline, 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, then the subject's PBMCs will be evaluated for integration site analysis (see below). If vector persistence is undetected for two consecutive visit assessments and the participant is ≥2 years post-infusion, samples for RCL and persistence of gene modified cells will be discontinued. All other assessments such as hematology and chemistry may also be stopped. Note: Samples for RCL must continue to be collected and archived annually for up to 15 years post infusion. The subject will continue to be followed by the investigator, local oncologist or local physician, 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 the LTFU whenever possible. If contact with the investigator becomes no longer feasible, follow up can be transitioned to a local physician, preferably an oncologist.

10.3.5. 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 integration site analysis. Integration site analysis assesses clonality and the possibility of insertional oncogenesis. This integration site analysis method, used in previous clinical trials[Hacien-Bey-Abina, 2014], uses sonic length quantitation, an accurate method of measuring relative clonal abundance [Berry, 2012]. Clonality is defined as follows: 1) monoclonality is 1 predominant clone at ≥5% of transduced T cells; 2) oligoclonality is defined as 2-5 predominant clones, each at ≥5% of transduced T cells; and 3) polyclonality is defined as no single predominant clone of ≥5% of transduced T cells.

If there is clonal dominance in the genetically modified T cell population (either monoclonality or oligoclonality) the persistence assessment will be repeated within 3 months on a new sample. If the repeated analysis demonstrates: 1) persistent monoclonality, 2) evidence of insertional oncogenesis or 3) clonal expansion, 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, and regulators of the findings. If the integration site analysis indicates polyclonality of the genetically modified T cell population, then screening continues as scheduled.

10.3.6. 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 focusses 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 exploratory endpoints) will be provided in the Reporting and Analysis Plan (RAP).

11.1. Study Populations

Intent-to-Treat (ITT) population: This population comprises all subjects who underwent leukapheresis. The ITT population is the primary analysis population for safety endpoints, where appropriate.

Modified Intent-to-Treat (mITT) population: All ITT subjects who received NY-ESO-1^{c259}T cell infusion comprises this population. The mITT population is the primary analysis population for efficacy endpoints and the primary analysis population for safety endpoints, where appropriate.

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

11.2. Statistical Methods for Interim Analysis

The enrolment rules at the interim analysis are defined based on a Bayesian predictive adaptive design [Lee, 2008] that allows the study to be monitored more frequently at multiple stages. The criteria will be based on a historical response rate of approximately 20% versus a response rate of interest of 40%, but the sample size is not powered for any formal hypothesis testing. Bayesian statistics will be employed to calculate the predictive probability that the response rate will be ≥40% and ≥20% at interim assuming a beta prior for the binomially distributed data. Predictive probability calculates the probability that the response rate will be ≥40% or ≥20% at the end of study given the responses that have already been observed. A weak prior beta (0.02, 0.08) is used, which is equivalent to the information present in 0.1 participant.

Interim analyses for ORR will start once at least 10 participants are evaluable. Participants are evaluable if they had at least 3 post baseline disease assessments or progressed or died or withdrawn from the study. The observed number of participants with confirmed investigator assessed response of PR or CR, per RESIST 1.1, will be compared with the stopping region in Table 12. Enrolment may stop if the stopping rule is met. Final decision will be based on the totality of data. For example, if there is 1 or no confirmed responses out of 10 evaluable subjects, enrolment may stop after review of all available data; if there are 2 or more confirmed responses out of 10 evaluable subjects, enrolment will continue up to 20 subjects.

Table 12 Futility Stopping Rules for Expansion Cohort

Number of Evaluable Subjects	Stop for Futility if No. of confirmed PR+CR is Less than or Equal to This Number	Prob. Of Continuing if True ORR=0.2	Prob. Of Continuing if True ORR=0.4
10	1	63.1%	95.1%
11	2	37.7%	87.4%

If expanded, interim analyses in the second cohort of 10 infused subjects (receiving the modified option 2 lymphodepletion regimen) may be conducted for internal decision making once at least 8 subjects are evaluable.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

11.3. Statistical Methods for Efficacy Endpoints

The study is not powered for either primary or secondary endpoints, hence there are no analyses to test hypotheses.

The primary analysis population for efficacy will be the mITT population. The ITT population will be used as a secondary population for analysis.

The following methods will be used for assessing efficacy at the end of the interventional phase. Full details will be provided in the RAP.

The primary endpoint for efficacy is Overall Response Rate (ORR) defined as the proportion of subjects with a confirmed complete response (CR) or partial response (PR) per RECIST v1.1 criteria by investigator assessment relative to the total number of subjects in the analysis population.

ORR will be summarized by two-sided 95% confidence intervals using exact and Wilson methods. 95% (Bayesian) credible intervals may also be used to summarize the ORR.

A sensitivity analysis will be conducted on ORR using the independent assessment of response per RECIST v1.1.

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

The ORR will be evaluated in the context of additional efficacy parameters such as time to confirmed response, duration of response, PFS and overall survival.

The secondary (efficacy) endpoints are defined below:

- Time to Response: the interval between T-cell infusion to the initial date of the confirmed response, in the subset of participants with a confirmed response of PR or CR.

- Duration of Response: the interval between the initial date of the confirmed response to the date of progressive disease or death, among subjects with a confirmed response of PR or CR.

- Progression Free Survival (PFS): the interval between the date of T cell infusion and the earliest date of disease progression or death due to any cause.

Duration of Response and Progression Free Survival endpoints will be summarized and displayed graphically using Kaplan-Meier (K-M) methodology to estimate the median, and the 25th and 75th percentiles if data warrant. Two-sided 95% confidence intervals will be produced. Overall Survival will be assessed at fixed time points such as 1 year and 2 years using K-M methods if data warrant.

The following censoring rules will be applied for the various time to event endpoints.

- Duration of response: subjects who are still alive and who do not have a documented disease progression date will be censored at the date of the last assessment.

- Progression free survival: subjects who do not have a documented date of disease progression or death will be censored at the date of the last assessment.

11.4. Statistical Methods for Safety Parameters

The primary analysis population for safety will be the ITT population, with the mITT used as necessary.

The following methods will be used for summarizing safety. Full details will be provided in the RAP.

Descriptive statistics will be provided for disposition, demographic, safety, imaging, and cytokine assessments. Continuous data will be summarized including 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 adverse events reported, vital signs measurements, clinical laboratory measurements and ECG recordings.

Adverse Events: All adverse events will be listed and coded by MedDRA. The number and percent of subjects reporting any adverse events will be tabulated by system organ class and preferred term. Adverse events with missing date of onset will be considered to have occurred on treatment. Adverse events will be further classified by toxicity (using CTCAE Version 4.0), relationship to treatment and seriousness. Tables and/or narratives of any death, or serious adverse event, including early withdrawals will be provided, should they occur.

Vital Signs: Vital signs will be listed for each subject, summaries of vital signs data over time may be provided.

Electrocardiogram: Electrocardiogram data will be listed for each subject. Fridericia's or Bazett's correction will be used to adjust QT for RR. Summaries of ECG intervals will be provided.

Clinical Laboratory Tests: Clinical chemistry, hematology, persistence, RCL, circulating cytokines and anti-NY-ESO-1^{c259}T antibody data will be listed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings (if applicable). Laboratory abnormalities will be graded using CTCAE version 4.0.

11.5. Other Analyses

PK (T cell persistence), pharmacodynamic, and biomarker analyses will be described in the RAP. PK data from this study may be combined with PK data from other studies and analyzed using population PK approaches. If performed, the population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

12. CLINICAL SUPPLIES

12.1. Packaging and Labelling

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

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

12.2. Standard Policies and Product Return

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

Sponsor or designee regarding any questions concerning the investigational product. At the end of the study or as dictated by protocol or process, all clinical supplies including partial and empty containers must be returned as indicated.

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

12.3. Storage and Handling

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

12.4. Product Accountability

The investigational product provided for this study is for use only as directed in the protocol. It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational product, so as to ensure that:

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

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

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Management

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

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

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

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

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

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

13.2. Case Report Forms

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

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

13.3. Site Documentation and Source Data

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

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

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

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

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

13.4. Data Retention and Availability

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

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

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

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

14. STUDY MONITORING

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

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

It will be the monitors (or designees) 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 (or designee) should have direct access to subject source documents to verify the entries on the eCRF. The investigator (or designee) agrees to cooperate with the monitor (or designee) to ensure that any discrepancies detected are resolved.

14.1. Audits and Inspections

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

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

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

Regulatory agencies may also inspect investigative sites during or after the study. The investigator (or designee) should contact GSK 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and any other site level committee deemed appropriate by the institution. Approval from each applicable committee will be received in writing before initiation of the study.

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

15.3. Local Regulations/Declaration of Helsinki

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

15.4. Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study related procedures being performed. All consent documentation must be in accordance with applicable regulations and ICH GCP. Documentation must include the dated signature of both the subject (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 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 enrolment 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 (or designee) must sign the protocol to confirm acceptance and willingness to comply with the study protocol.

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

15.7. Study Suspension, Study Termination and Study Completion

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

If the investigator stops/terminates study at their site the Sponsor must be notified. The Sponsor will ensure that regulatory agencies and IRBs/IECs are notified as appropriate.

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

15.8. Public Posting of Study Information

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

15.9. Clinical Study Report

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

15.10. Publication Policy

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

16.1. List of Abbreviations and Definitions of Terms

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

Abbreviations and Specialist Terms

ABW	Adjusted Body Weight
ACS	Acute Coronary Syndrome
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ASBMT	American Society for Blood and Marrow Transplantation
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ATG	Antithymocyte globulin
BBB	Bundle branch block
BP	Blood pressure
BSA	Body surface area
CAR	Chimeric Antigen Receptors
CKD-EPI	Chronic kidney disease Epidemiology Collaboration
CMV	Cytomegalovirus
cm	centimeter
CR	Complete Response
CrCl	Creatinine clearance
CRP	C-reactive protein
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CT	Computerized tomography
CTA	Clinical Trials Assay
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DILI	Drug-induced liver injury
dL	deciliter
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular filtration rate
EMG	Electromyography
FCM	Flow cytometry
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin embedded
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGTP	Gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
GvHD	Graft-versus-Host Disease

Gy	Grey
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IBW	Ideal body weight
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
ID	Identifier
IHC	Immunohistochemistry
IND	Investigational New Drug application
INL	Investigator Notification Letters
INR	International Normalized Ratio
IO	Insertional Oncogenesis
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat population
mITT	Modified Intent-to-Treat population
IV	Intravenous
Kg	kilogram
LDH	Lactic acid dehydrogenase
LTFU	Long term follow-up
max	Maximum
mg	miligram
MHC	Major histocompatibility complex
min	Minute/Minimum
mL	Mililiter
MRCLS	Myxoid/round cell liposarcoma
MRI	Magnetic resonance imaging
MUGA	Multiple-gated acquisition scan
NCI	National Cancer Institute
NIH	National Institutes of Health
NS	Normal Saline
OS	Overall survival
OTC	Over the counter
ORR	Overall response rate
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive Disease
PET	Positron emission tomography
PFS	Progression free survival
PT	Prothrombin time
PTT	Partial thromboplastin time
PR	Partial response
RAP	Reporting and analysis plan
SAE	Serious adverse event
Scr	Serum Creatinine
SD	Stable Disease
SIN	Self-inactivating
SOP	Standard operating procedure
SPM	Study Procedures Manual
SUSAR	Suspected, unexpected serious adverse reaction
TCR	T cell receptors
TILs	Tumor-infiltrating lymphocytes
RAC	Recombinant DNA Advisory Committee
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors

RNA	Ribonucleic acid
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of childbearing potential

Trademark Information

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None

16.2. ECOG Performance Status

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.

16.3. Laboratory Tests and ECG

<table>
<tr><th colspan="2">Hematology, Chemistry and Urinalysis Variables</th></tr>
<tr><th>Clinical Chemistry</th><th>Hematology</th></tr>
<tr><td>Calcium
Phosphorus
Magnesium
Albumin
Bilirubin
Alanine aminotransferase
Aspartate aminotransferase
Alkaline phosphatase
LDH</td><td>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)</td></tr>
<tr><td rowspan="2">Sodium
Potassium
Bicarbonate
Creatinine
Chloride
Glucose
BUN or Urea</td><td>Lymphocyte subsets</td></tr>
<tr><td>Lymphocyte subsets including CD3 T cell (absolute) count</td></tr>
<tr><th>Other Tests</th><th>Coagulation Screen</th></tr>
<tr><td>Uric Acid
C-reactive protein</td><td>Prothrombin time or International Normalized Ratio
Activated partial tissue thromboplastin time</td></tr>
<tr><th>Pregnancy Test</th><th>Thyroid Function Tests</th></tr>
<tr><td>Serum beta-HCG or Urine test</td><td>Thyroid Stimulating Hormone (TSH)
Free T3
Free T4</td></tr>
<tr><th>Urinalysis</th><th>Microbiology</th></tr>
<tr><td>Glucose
Ketones
Specific gravity
Protein
Blood
Microscopy
Bilirubin
pH</td><td>Infectious disease screen
HIV 1+2 antibody
Hepatitis B surface antigen
Hepatitis B core antibody – if positive, test for HBV DNA
Hepatitis C antibody – if positive, test for HCV RNA HTLV 1+2 IgG
CMV IgG
EBV (EBNA)
Treponema (Syphilis)
Viral reactivation
CMV DNA PCR – peripheral blood for detection of reactivation. In the event of suspected end organ CMV disease a biopsy may be required</td></tr>
<tr><th colspan="2">ECG Parameters</th></tr>
<tr><td colspan="2">Heart Rate
Heart Rhythm
PR Interval
RR Interval
QRS Interval
QTc Interval (if initial reading is abnormal, the average of 3 readings over 5 minutes; Fridericia’s or Bazett’s correction)</td></tr>
</table>

16.4. RECIST 1.1 Criteria for Evaluating Response in Solid Tumors

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

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

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

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

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

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

Measurable lesions

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

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

Measurable lesions

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

- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.

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

Non-measurable lesions

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination 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. The appearance of one or more new lesions is also considered progression. Determination of PD will not be made prior to the Day 60 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)

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'.

Evaluation of non-target lesions

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

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

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

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

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

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

New lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings

thought to represent something other than tumor, especially when the subject's baseline lesions show partial or complete response).

- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

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

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

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

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

- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
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.

Where progression is equivocal, confirmation of PD is required unless there is an immediate medical need to initiate anti-cancer therapy before a confirmatory scan can be arranged.

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

16.5. Liver Safety Required Actions and Follow up Assessments

Liver Safety: Required Actions and Follow-up Assessments.

Level 1 Monitoring

In the event that the subject develops elevations in 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, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize 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)
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:** **For bilirubin or INR criteria:** • 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 (CPK) and lactate dehydrogenase (LDH). • 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 kidneymicrosomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized 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

16.6. Summary of Changes from Protocol Version 1.0 to Version 2.0

Section of Version 1.0	Section of Version 2.0	Change
Title	**Title**	**Change of title to reflect alteration in scope to a pilot study**
Synopsis	Synopsis	Updated with new study title, phase, details of long-term follow up protocol, study duration, number of subjects, statistical methodology, editorial changes
1.2	1.2	Updated historical data for IP
1.4	1.4	Change to rationale to reflect pilot study
3.1	3.1	Study design changed to reflect patient numbers. Updated definition of inoperable disease. Clarification on consent process.
3.2.1	3.2.1	Definition of screening and interventional phases added. Obsolete wording on futility removed.
3.2.3	3.2.3	Time of manufacturing amended to reflect product release only after full release testing is performed.
3.2.4	3.2.4	Reference updated
3.3	3.3	Updated with new design and rationale for potentially expanding study enrolment
3.4	3.4	Number of clinical sites updated to reflect change in study design
3.5.1	3.5.1	References updated
3.5.3	3.5.3	Risk: benefit updated to reflect change to pilot study
4.1	4.1	Definition of “inoperable” included to clarify criterion Detail added to clarify Gilbert syndrome Biopsy requirement updated Requirements for contraception moved to own section. Wording added to allow for country- specific requirements.
4.2	4.2	Explanation added to clarify wash-out periods are prior to leukapheresis and lymphodepletion. Radiotherapy wording updated to specify palliation to lesions rather than organs. Requirement for triplicate ECGs moved to ECG / lab test section.
4.3	4.3	Information on long-term follow up protocol added
4.4	4.4	Criteria for subject withdrawal updated
5.1	5.1	Recommendations for clinical care of leukapheresis patients added – minimum recommended lymphocyte and T cell counts. Wording for hypocalcemia prophylaxis updated.
5.2	5.2	Instructions for administration of lymphodepleting chemotherapy updated. Volume of chemotherapy infusions updated. Clarification on timing of T cell infusion added.
5.2.2	5.2.2	Recommended regimen for Mesna updated
6	6	Timing for concomitant medication collection start / stop clarified
6.1	6.1	Information on long term follow up protocol provided
-	6.2.1	New section defining females of childbearing potential and requirements for contraception added
7	7	Information on assignation of Subject ID and long term follow up protocol provided
7.1	7.1	Information on centralized HLA screening provided
7.3	7.3	Lymphocyte subsets test added Disease history collection clarified – Screening 2 only Concomitant medications clarified – Screening 2-onwards Renal function testing requirements updated
7.4.2	7.4.2	Typo corrected
7.4.9	7.4.9	Clarification on independent response assessment provided
7.4.10	7.4.10	Further information on long term follow up provided
new	8.2.1	Information on prophylaxis against pneumocystis carinii pneumonia provided
new	8.2.2	Information on prophylaxis against HSV and VSV provided
new	8.2.5	Information on screening for Treponema provided

Section of Version 1.0	Section of Version 2.0	Change
new	8.2.6	General recommendation for anti-microbial prophylaxis provided
9.1	9.1	Collection period for AEs and SAEs redefined
9.4	9.4	Information on long term follow up protocol added
9.7	9.7	Clarification on recommendations for breastfeeding provided Information on long term follow up protocol added
new	10.1	Information on data safety monitoring plan added
new	10.2	Study stopping rules added
10.3.2	10.3.2	Actions on positive RCL test updated
10.3.4	10.3.4	Clarification on provision of LTFU follow-up provided
10.3.5	10.3.5	Information on specifics of testing for insertional oncogenesis added
11.1	11.1	Study populations clarified
11.2	11.2	Information on statistical basis for analysis of the updated pilot study provided. Information on Bayesian and frequentist methods for analysis of ORR added Details provided on potential expansion of the study beyond n=10 added
11.3	11.3	Statistical methods for assessing endpoints updated
11.4	11.4	Statistical methods for assessing safety updated
12.2	12.2	Editorial changes
12.3	12.3	Storage temperature requirements updated
16.1	16.1	Glossary updated
16.3	16.3	Laboratory test and ECG table updated to allow BUN instead of urea testing. Lymphocyte subsets test added Treponema test amended to broaden methodologies allowed QT testing clarified
16.4	16.4	Details of confirmatory scans updated
17	17	References updated

16.7. Summary of Changes from Protocol Version 2.0 to Version 3.0

Section of Version 2.0	Section of Version 3.0	Change
Synopsis	Synopsis	Updated exclusion criteria to include revised therapy washout periods required prior to leukapheresis and lymphodepletion
4.2	4.2	Updated exclusion criteria to include revised therapy washout periods required prior to leukapheresis and lymphodepletion
5.2.1	5.2.1	Corrected typographical error – full fludarabine dose was previously at GFR >80mL/min which left the dose required at exactly 80mL/min undefined; changed to ≥80 mL/min
7.3	7.3	Schedule of procedures updated Adverse Events to be collected from Visit 2 in line with protocol Section 9.1 Additional column added to differentiate Year 1 post-infusion assessments from subsequent assessments and allow for clarified explanation of research sampling at these time points. Footnotes updated: 1) Updated to clarify that only Visit 2 screening assessments are required to occur within a specified time prior to leukapheresis 5) Typographical error corrected; vital signs are to be measured at time points after start of T cell infusion, not end of infusion
7.3	7.3	7) Timing of response / progression confirmatory scan clarified 17) Updated to include timings for baseline biopsy specified in Section 7.5.3 Additional footnotes added: Specifies that Day 1 ECG is to be performed pre-infusion Provides timings for persistence testing stated in Section 10.3.4 Provides timings for RCL testing stated in Section 10.3.4 Provides visit frequency for subjects >1yr post-infusion
7.4.9	7.4.9	Timing of response / progression confirmatory scan clarified

Section of Version 2.0	Section of Version 3.0	Change
16.3	16.3	HBV surface antigen added in line with inclusion / exclusion criteria Information added on when triplicate ECG testing is needed

16.8. Summary of Changes from Protocol Version 3.0 to Version 4.0

Section of Version 3.0	Section of Version 4.0	Change
3.5.3	3.5.3	Update to risk assessment to add additional risk of Guillain-Barré syndrome and other demyelinating neuropathies.
4.2	4.2	Addition of Prior or active demyelinating disease as an exclusion criterion.
9.3	9.3	Addition of all cases of Guillain-Barré syndrome or acute demyelinating neuropathy as a reportable SAE within 24 hours.
N/A	10.1.1	Addition of Mandated Study Pause due to GBS
N/A	10.3.6	Addition of Monitoring and Management for Demyelinating Neuropathy and other Neurological events

16.9. Summary of Changes from Protocol Version 4.0 to Version 5.0

Rationale for Amendment

The purpose of this amendment is to provide clarification on definitions of enrolment and intent to treat population.

Summary of Changes

The following details the changes made for the current protocol version 05. Bolded text has been added and text with strikethrough has been deleted. Minor typographical or editorial changes were also made, none of which impact the overall content or interpretation of the protocol.

Change 01

Section: Synopsis, Methodology

Initially, 10 subjects will be enrolled treated/infused in this study. If further characterization of the treatment in this indication is required, up to a further 10 subjects may be enrolled treated/infused. The Sponsor may also decide to close the study at any time based on safety or efficacy.

Change 02

Section: Synopsis, Number of subjects

The target enrolment for this trial is up to 20 subjects, depending on emerging data. Up to 20 subjects may be enrolled treated/infused in total.

Change 03

Section: Synopsis, Statistical Methodology

After 10 evaluable subjects, response will be evaluated using Bayesian posterior predictive probabilities to inform clinical decision making to continue enrolment to up to 20 evaluable subjects.

The primary analysis population for safety and efficacy will be the intention to treat population (ITT) defined as all subjects who enrolled and were apheresed in this study.

Change 04

Section 3.2.3 T-Cell Manufacturing (2nd paragraph)

At the end of the culture, cells are depleted of magnetic beads, washed, concentrated, and cryopreserved. Release testing takes approximately an additional 8-10 days 4 weeks. Therefore, cell product typically is ready to be returned to the site approximately 28 42-45 days after subject apheresis.

Change 05

Section 3.3 Target Enrolment and Study Duration

A target enrolment of 10 subjects infused with potential expansion up to 20 subjects is considered appropriate for evaluating preliminary efficacy (antitumor activity) and safety in this phase I/II study of subjects with a rare, orphan disease.

Potential subjects will first sign a screening consent to screen for HLA and antigen testing. It is expected that approximately 50% of subjects will be HLA negative, and 20% of these subjects will be NY-ESO negative. Therefore, it

is expected that up to 60 subjects may sign the screening consent. Once HLA and antigen testing are confirmed, subjects will return for the second screening visit, at which time the treatment consent will be signed, and the remainder of eligibility requirements will be verified. Enrolled subjects will be considered those subjects who sign the treatment consent, meet all eligibility requirements, and undergo apheresis. Based on information gathered from the pilot sarcoma study, it is expected that there will be some subjects who undergo apheresis but do not receive manufactured cells. Therefore, in this study, approximately 26 subjects may be enrolled in order to obtain the target number of 20 subjects treated with manufactured product. Up to 13 subjects may be enrolled in order to obtain the target number of 10 subjects treated with manufactured product in cohort 1, and up to 13 subjects may be enrolled in order to obtain the target number of 10 subjects treated with manufactured product in cohort 2. Once the target number of patients have manufactured product in each cohort, the study will be closed for enrolment and apheresis. In the event that a subject has manufactured product and is not able to receive treatment, an apheresis slot may then be opened for a screen positive patient to be enrolled.

4th paragraph:

The confirmed overall response rate per RECIST V1.1 by independent investigator review will be evaluated after the first 10 enrolled subjects have been treated and the last ongoing subject has at least 8 12 weeks of follow up or has progressed.

Change 06

Section 11.1 Study Populations

Intent-to-Treat (ITT) population: This population comprises all eligible subjects who were enrolled in the trial (i.e., all subjects who signed the treatment informed consent and underwent apheresis). The ITT population is the primary analysis population for efficacy and safety evaluations.

Change 07

Section 11.2 Statistical Methods for Interim Analysis

Participants are evaluable if they had at least 2 3 post baseline disease assessments or progressed or died or withdrawn from the study.

16.10. Summary of Changes from Protocol Version 5.0 to Version 6.0

Rationale for Changes:

- The purpose of this amendment is the following:
- Addition/clarification of delayed AE definition
- Revised guidelines for the management of CRS
- Revised guidelines for the management of encephalopathy syndrome
- Adjustment to lymphodepletion regimen for safety purposes
- Various clarifications and administrative updates

Additions are marked in red, deletions are marked with ~~strikethrough.~~

Change 1 Synopsis

Option 1 (first 10 subjects) will involve lymphodepleting chemotherapy with fludarabine and cyclophosphamide on Days -7 to -5 and the study therapy by a single intravenous infusion on Day 1. Option 2 (second 10 subjects) will involve lymphodepleting chemotherapy with fludarabine on Days -8 to -5 and cyclophosphamide on Days -7 to -5 and the study therapy by a single intravenous infusion on Day 1.

Change 2 Synopsis

Dose and regimen for lymphodepleting chemotherapy will be adjusted for subjects ≥60 years of age.

Change 3 Synopsis

The target ~~treatment~~ enrolment for this trial is up to 20 subjects treated, depending on emerging data. Up to 20 subjects may be treated/infused in total.

Change 4 Synopsis

Exclusion #2: Radiotherapy within the following periods prior to leukapheresis or lymphodepleting chemotherapy (study team should consider prior cumulative radiotherapy totaling <25% of body surface area).

Change 5 Synopsis

Exclusion #9: Ongoing or active infection. EBV and CMV IgG seropositive patients who have a positive PCR

Change 6 Synopsis

The primary analysis population for safety ~~and efficacy~~ will be the intention to treat population (ITT), where appropriate, defined as all subjects who enrolled and were apheresed in this study and the modified intention to treat population (mITT), where appropriate, defined as all subjects who were treated in this study. The primary analysis population for efficacy will be the mITT population.

Change 7 Section 2, Table 1

- AEs, including SAEs and AESIs

Change 8 Section 3.2.4

Age related modifications to the lymphodepletion regimen will be made as outlined in Section 5.2.

Change 9 Section 3.3

Expansion from n=10 to a maximum of n=20 may be done to better characterize safety, efficacy and tolerability, based on the clinical evaluation of the emerging data (See Section 11). In addition, more subjects may be enrolled for those who do not receive the minimum cell dose or

who do not receive the T-cell infusion ~~may be replaced~~ to better characterize safety, efficacy and tolerability as part of this expansion.

Change 10 Sections 3.5.1, 3.5.2

Safety profile updated based on latest IB.

Change 11 Section 4.2

Exclusion #2: Radiotherapy within the following periods prior to leukapheresis or lymphodepleting chemotherapy (study team should consider prior cumulative radiotherapy totaling <25% of body surface area).

Change 12 Section 4.2

Exclusion #9: Ongoing or active infection. EBV and CMV IgG seropositive patients who have a positive PCR

Change 13 Section 4.3

A subject will be considered to have completed the interventional phase of the study when he/she has confirmed progression of disease (see Section 7.4.10 for tumor response assessments), withdrawal of consent, death, or 2 years after NY-ESO-1^{C259}T cell infusion, whichever is shorter.

Change 14 Section 4.3.1

Long-Term Follow-up – new section

Change 15 Section 5.2

Dose and regimen for lymphodepleting chemotherapy is adjusted for participants ≥60 years of age, as specified in Table 2, Option 2. For participants with documented history of severe and/or 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.

Change 16 Table 2, Option 2 – lymphodepletion dose for participants ≥60 years old added

Change 17 Section 5.2.1

This adjustment needs to be applied to all doses. Patients ≥ 60 years of age receiving an age adjusted dose, will have the renal adjustment applied to the modified dose for age.

Change 18 Section 6.3.1

~~Subjects randomized to Arm 2 must also use effective contraception for at least 4 months after the last dose of pembrolizumab.~~

Change 19 Section 7

Administrative updates

Change 20 Section 7.4, Table 4

Multiple changes within SoA

~~CARTOX~~ ICE

Cytokine analyses ~~& humoral anti-infused cell response~~

Anti-NY-ESO-1 TCR Antibodies (Immunogenicity Sample) (Day 1, Wk 3, Wk 5, Wk 8, Wk 12, Wk 24, M9, M12, Completion or WD)

Exosome and ctDNA collection (liquid biopsy) (Additional at D8 & W4)

Change 21 Section 7.4, Table 4 footnotes

#13. If cytokine release syndrome is suspected, CRP levels should be measured every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.

#17. Core needle biopsies for research are ~~planned~~ required at baseline, Week 8, and at progression, with the exception of subjects for whom there is no safely accessible tumor tissue. Archival tissue may be used for screening. The baseline biopsy ~~may~~ should be collected any time between two months and 2 weeks prior to the start of lymphodepleting chemotherapy.

#19. Pre-infusion, Week 3, Week 8, and Week 12 blood collection is for both Cytokine and Immunogenicity responses, and is collected in one 3 ml tube. If CRS is suspected, cytokines should be collected every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.

~~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.~~

#20. Vector copies for safety samples are collected Day 1 (pre-infusion) and then every 6 months post-infusion up to 5 years (Section 10.3.4 for more details). For RCL, samples are collected Day 1 (pre-infusion), and at Week 12, Week 24, and 1 year post-infusion and then annually for up to 15 years.

~~Vector copies for safety samples are collected Day 1 (pre-infusion) and then every 6 months post-infusion up to 5 years. For RCL, samples are collected Day 1 (pre-infusion), and at Week 12, Week 24, and 1 year post-infusion and then annually.~~

#24. ~~CARTOX 10~~ 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 have ~~ES~~ ICANS, the ~~CARTOX 10~~ ICE should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

Change 21 Section 7.4.9

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

~~CARTOX-10~~ Immune Effector Cell-Associated Encephalopathy (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 subject is found to have ~~ES~~ ICANS, the ~~CARTOX-10~~ ICE should be used at least twice per day until resolution or stable.

Change 22 Section 7.4.10

~~For subjects who have new lesions, response by irRECIST (Nishino 2013) will be assessed by the investigator for exploratory purposes. 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.~~

Change 23 Section 7.5

- ~~Luminex~~ MSD to measure serum cytokine levels
- Tissue analysis for immune cell infiltrate and functional biomarkers (by single or multiplexed IHC) and gene expression profile (including by Nanostring or next-gen sequencing ofRNA)
- Tissue analysis to determine the evolution of the mutation profile of the tumor over the course of the therapy by DNA sequencing analysis

Change 24 Section 7.5.3 – change of core needle biopsies from requested to mandated

Change 25 Section 7.5.4

Quantitation of NY-ESO-1^{c259}T TCR+ cells by PCR of transgene from DNA extracted from frozen PBMC. This will be used as a measure of pharmacokinetics.

Change 26 Section 7.5.6 – testing clarifications

Change 27 Section 8.5, Table 6

entire table updated

CRS grading updated

Change 28 Section 8.7.3

Management of Guillain-Barré Syndrome (GBS) section added with specific instructions on assessments, grading, and treatment.

Change 29 Section 9.1

All AEs and SAEs will be collected and reported from the time ~~the subject signs a treatment informed consent form~~ of leukapheresis until the subject has completed the interventional phase of the study. Regardless of study end for a participant, all SAEs must be collected through 90 days following T cell infusion, or 30 days following T cell infusion if the participant initiates new anticancer therapy, whichever is earlier.

Change 30 Section 9.4

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.

~~Subjects with confirmed disease progression will transfer to a LTFU protocol GSK208750 (ADP-0000-2) for continued monitoring of gene therapy related adverse events. Emergence of any of the following new clinical conditions reported or observed and the action taken will be reported to the Sponsor:~~

Change 31 Sections 9.8, 9.8.1

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

Section updated to reflect updated management guidelines and grading of ICANS

Change 32 Section 10.2

Any event of Guillain-Barre syndrome (GBS) as diagnosed by a neurologist according to diagnostic guidance for GBS [Fokke, 2014].

Change 33 Section 10.3.4

Note: Samples for RCL must continue to be collected and archived annually for up to 15 years post infusion.

Change 34 Sections 11.1, 11.3, 11.4

The ITT population is the primary analysis population for safety endpoints, where appropriate ~~efficacy and safety evaluations~~.

The mITT population is the primary ~~secondary~~ analysis population for efficacy endpoints and the primary analysis population for ~~and~~ safety endpoints, where appropriate.

The primary analysis population for efficacy will be the mITT population. The ~~m~~ITT population will be used as a secondary population for analysis.

The primary analysis population for safety will be the ITT population, with the mITT used as necessary.

16.11. Summary of Changes from Protocol Version 6.0 to Version 7.0

Rationale for Changes:

The primary purpose of this amendment is to update the primary endpoint of ORR to be based on investigator assessment rather than independent reviewer assessment.

The following table details all changes and rationale:

Study 208469: List of Changes included in Protocol Amendment 6		
Section	**Change**	**Rationale**
Section 2	Updated primary endpoint of ORR to be based on investigator assessment rather than independent reviewer assessment	Align method of assessment of primary endpoint of ORR for overall analysis with that for interim analysis to provide consistency between the two analyses
Section 2	Inserted secondary endpoint of ORR as assessed by independent review	Clarify that secondary ORR efficacy endpoint assessment to be conducted by independent review
Section 2	Inserted secondary endpoint for PK profile	Clarify terms for monitoring persistence of NY-ESO-1c259T cells
Section 2	Removed secondary endpoint for development of companion diagnostic assay and removed references to companion diagnostic assay throughout protocol amendment	Clarify that assay development is not being undertaken
Section 2	Exploratory objective /endpoint - Replaced term “persistence” with “PK profile”	Provide greater clarity for what parameters are to be assessed
Section 2	CCI [redacted]	
Section 2	Updated pharmacogenetic endpoint	Expand analysis from cytokine genes to entire genome – consistent with program objective/endpoint
Section 3.1, Section 4.3	Included guidance for monitoring of response post 2-years on trial	Provide guidance to permit ongoing monitoring of responding patients supporting broader understanding of drug activity
Section 3.2.3	Updated background information for GSK3377794 in T-cell manufacturing section	Provide more comprehensive description of GSK3377794 and ongoing clinical trials
Section 3.3	Update plans for enrollment into Option 1 and update definition of study complete	Provide clarification to enrollment plans and to definition of study completion
Section 3.3	Updated definition of evaluable subjects in Section 3.3 to match that provided in Section 11.2 Interim Analysis	Establish consistency
Section 3.3	Deleted statement in Section 3.3 that continuous interim assessment of participants beyond 10 would “be used to continuously assess ORR and inform decisions regarding enrollment of additional subjects”.	Clarify to align description of interim analyses with those planned following introduction of the high lymphodepletion regimen for the expansion cohort in amendment #2:
Section 3.5.2	Updated Risk Assessment section with safety data from most recent GSK3377794 Investigator Brochure Version 12	Ensure most up-to-date risk information is included in protocol

Study 208469: List of Changes included in Protocol Amendment 6		
Section	**Change**	**Rationale**
Section 3.5.2.	Included US adopted name (USAN) of GSK3377794 – letestregene autoleucel (lete-cel as appropriate throughout protocol	Include USAN drug name
Section 4.1, Section 6.3.1	Updated requirements for female contraception	Provide most up-to-date program-level guidance for duration of female subject contraception use
Section 4.3	Clarified definition of completion of interventional phase	Prior definition unclear and not sufficiently comprehensive
Section 4.3	Clarified completion of study definition	Prior definition unclear and not sufficiently comprehensive.
Section 6.1	Clarified consequence of subject receiving new anti-cancer therapy while on study	Provide clear description of impact of active patient receiving anti-cancer therapy while continuing in the interventional portion of the study.
Section 7.3, Table 4	Corrected heading to column describing activities to be completed in Years 1 and 2. Prior title not consistent with safety assessment intent and tumor assessment scan interval defined in Section 7.4.10	Ensure correct safety and tumor assessment frequency included in protocol.
Section 7.3, Table 4	Added a footnote clarifying frequency of sample collection for TCR antibody analyses	Ensure correct sample collection frequency included in protocol
Section 7.4.10, multiple protocol sections	Removed requirement for confirmation of disease progression	Confirmation of disease progression not required by RECIST v 1.1. Not updated in prior protocol amendment 5 when irRECIST was removed from protocol.
Section 11.1	Clarified and made consistent descriptions of ITT and mITT populations (with no change to population definitions)	Improve protocol text used to describe these two populations.
Section 11.1	Updated definition of Intent-to-Treat population	Define ITT population and clarify meaning of “enrolled”
Section 11.2	Added statement describing planned second interim analysis in “at least 8 evaluable” in the high lymphodepletion cohort.	Clarify to align description of interim analyses with those planned following introduction of the high lymphodepletion regimen for the expansion cohort in amendment #2:
Section 11.3	Clarified description for Time to Response endpoint	Clarify which subjects suitable for this analysis. Analysis had previously been incorrectly described as a survival analysis.
Section 11.3	Updated information for secondary efficacy endpoints throughout section	Clarify which efficacy endpoints are used in study
Throughout amendment	Clarified text for improved ease of understanding and corrected formatting	Enhance reader comprehension and improve document readability
Throughout amendment document	Format of entire document updated from Adaptimmune style to GSK standard protocol format	Bring document into compliance with GSK formatting standards

16.12. Summary of Changes from Protocol Version 7.0 to Version 8.0

The primary purpose of this amendment is to add the potential for a second infusion for eligible subjects with sufficient residual cell product.

The following table details all changes and rationale:

Study 208469: List of Changes included in Protocol Amendment 7		
Section	**Change**	**Rationale**
Section 7.6	Incorporated Section 7.6 describing potential for retreatment for subjects who meet specific criteria and have sufficient residual cells	Provide the opportunity for subjects who have a confirmed CR or PR or SD ≥3 months, have disease progression >3 months post T cell infusion, and have adequate residual cells for a second NY-ESO-1^{c259}T cell infusion to receive a second T cell infusion. The intent is to provide those patients who have benefitted from the drug product a retreatment opportunity in a setting where efficacy, safety, and tolerability can be followed as exploratory objectives.

16.13. Summary of Changes from Protocol Version 8.0 to Version 9.0

The primary purpose of this amendment is to make changes to protocol in reference to Dear Investigator Letter dated 03 May 2021 and Protocol and ICF clarification memorandum dated 11 May 2021 regarding mitigations put in place on active studies of GSK3377794 (letetresgene autoleucel, lete-cel), following the recent SAEs of fatal neutropenia (1 event) and decreased vision (1 event).

The following table details all changes and rationale:

Study 208469: List of Changes included in Protocol Amendment 8		
Section	**Change**	**Rationale**
Synopsis: Subject inclusion criteria Section 4.1, Subject Inclusion Criteria	Updated Inclusion criterion 14, Definitions of Adequate Organ Function, Renal: provided further guidance on assessing accurate Renal function with below changes: 1. Guidance for assessment of Renal function in participants who are ≥18 and <65 years of age 2. Guidance for assessment of Renal function in participants who are ≥65 years of age	Additional guidance is provided for precise calculations of Creatinine clearance and assessment of renal impairment prior to initiating lymphodepleting chemotherapy. Dose adjustments for fludarabine and cyclophosphamide will be performed based on the revised calculations using the guidelines provided through this change in the protocol.
Synopsis: Subject Exclusion Criteria Section 4.2, Subject Exclusion Criteria	Removed (study team should consider prior cumulative radiotherapy totalling <25% of body surface area) and replaced it with Participant has received ≥50 Gy to a significant volume of the pelvis, long bones or spine, or a cumulative dose of radiation that, in the investigator's opinion would predispose patients to prolonged cytopenia after lymphodepletion	The intent of this criterion was to exclude subjects who have undergone radiotherapy that exceeded a minimum bone marrow exposure. The change will apply to any radiotherapy (ie. including palliative, adjuvant or neoadjuvant); this exclusion is modified in the protocol amendment to further quantify exposure to aid in assessment of bone marrow reserve.
Section 5.2, Lymphodepleting Chemotherapy	Further guidance provided on identifying participants requiring dose modifications for lymphodepleting chemotherapy. Table 2, footnote 1: clarification provided on fludarabine dose adjustment. Table 3: CrCl range of 30 – 80 mL/min is divided into >50 – 80 mL/min with corresponding fludarabine dose of 20 mg/m^2 and 30 – 50 mL/min with corresponding fludarabine dose of 15 mg/m^2. Added section 5.2.2, Cyclophosphamide Dose Adjustment.	This clarification allows identifying participants who may require dose modifications due to other reasons. For Clarification Further guidelines were provided for accurate calculation of creatinine clearance and dose adjustment for lymphodepleting chemotherapy. Additional guidelines provided for cyclophosphamide dose adjustment and additional guidelines for calculating ideal and adjusted body weight..

Study 208469: List of Changes included in Protocol Amendment 8		
Section	**Change**	**Rationale**
Section 9.3, Reporting Serious Adverse Events	Addition to SAE defining criterion of AE of special interest: Neutropenia grade 4 lasting ≥28 days	Neutropenia grade 4 lasting ≥28 days will now be considered an AE of special interest, and must be reported to the Sponsor within 24 hours, as per established process outlined in protocol section 9.3

16.14. Summary of Changes from Protocol Version 9.0 to Version 10.0

The primary purpose of this amendment is to make changes to protocol in reference to Dear Investigator Letter dated 21-Oct-2021 and Protocol and ICF clarification memorandum dated 25-Oct-2021 regarding mitigations put in place on active studies of GSK3377794 (letetresgene autoleucel, lete-cel).

The following table details all changes and rationale:

Study 208469: List of Changes included in Protocol Amendment 9		
Section	**Change**	**Rationale**
Section 3.5.2. Risk Assessment	Updated Risk Assessment to include the risk of Cardiac Arrest and reference to guidelines for management of patients with significant cardiac risk factors and known lung metastasis. Updated guidelines for infection prophylaxis	Clarification provided based on mitigation plan in relation to the safety events.
Synopsis: Subject Exclusion criteria Section 4.2, Subject Exclusion Criteria	Updated Exclusion criterion 9, to include clarification for active ongoing infections including but not limited to systemic fungal infections	Clarification provided based on mitigation plan in relation to the safety events.
Section 7.3 Schedule of Assessments	Footnote 7: Added clarification on requirement for ECHO/MUGA at the onset of CRS and the need for continuous temeletry monitoring for a minimum of 3 days. Footnote 21: Added clarification on frequency of ECG and requirement for ECG in patients with clinically significant cardiovascular risk factors	To monitor for cardiovascular events in patients with clinically significant cardiovascular risk factors.
Section 7.4.8 Cardiac Assessments	Included further detail for assessment of patients with clinically significant cardiovascular risk factors, including clinical evaluations prior to lymphodepletion	To monitor for cardiovascular events in patients with clinically significant cardiovascular risk factors.
Section 7.4.9 Pulmonary Assessments	Added section for pulmonary assessments in patients with known lung metastasis. Provided guidelines for close monitoring of such participants post-infusion and if CRS is suspected	To monitor for safety events in patients with lung involvement.
Section 8.2 Infection Section 8.2.6 Other Anti-Microbial Prophylaxis	Included clarification for increased surveillance of participants with indwelling catheters to monitor for catheter-associated infections. Guidelines for close monitoring for cardiac function in participants requiring treatment with anti-microbials associated with cardiac toxicity	To monitor for catheter-associated infections. To monitor for cardiac toxicity associated with anti-microbial use
Section 8.3 Hematologic and Blood Product Support	Added guidelines for blood product support for low platelet count in in-patient and out-patient settings.	For management of thrombocytopenia in in-patient and out-patient setting.

Section 8.5 Management of Cytokine Release Syndrome	Added guidelines for managing CRS in patients with clinically significant cardiovascular risk factors. Added guidelines for cardiac assessments during suspected CRS.	To monitor for cardiovascular events in patients with CRS

16.15. Summary of Changes from Protocol Version 10.0 to Version 11.0

The primary purpose of this amendment is to make changes to protocol section 7.6 to remove the language around anticancer therapies post-progression after first infusion of lete-cel (GSK3377794).

The following table details all changes and rationale:

Study 208469: List of Changes included in Protocol Amendment 10		
Section	**Change**	**Rationale**
Synopsis and Section 2.1 Trial Objectives and Endpoints	Updated table to reflect Exploratory Efficacy and Safety Objectives to align with protocol Section 7.6.7. Objectives	For consistency between protocol main body and synopsis sections
Section 7.5.1. Pharmacogenetics Sample	Updated language regarding potential usage of pharmacogenetics sample to investigate the association of candidate or genome-wide genetic variants with efficacy and safety.	Updates made in order to align with all lete-cel (GSK3377794) studies.
Section 7.6. Retreatment	Included additional clarification on second lete-cel infusion eligibility requirement. • Inclusion of language to allow patients to receive second lete-cel infusion after receiving subsequent anticancer therapies post-progression from first lete-cel infusion • Inclusion of language to allow collection of biopsy sample post-progression from recent anticancer therapy for eligibility determination for second lete-cel infusion	To allow second infusion in patients who have achieved clinical benefit from first lete-cel infusion and have received subsequent anticancer therapies post-progression from first lete-cel infusion
Section 10.3.1. Testing for RCL in Clinical Studies Section 10.3.4. Test for persistence of gne marked cells in clinical studies	Updated language regarding testing for persistence and RCL in patients who have two consecutive negative test results and are 2 years and beyond post lete-cel (GSK3377794) infusion.	Updates made in order to align with all lete-cel (GSK3377794) studies.

17. LIST OF REFERENCES

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