Protocol Amendment 4

Study ID: 209012 Core

Official Title of Study: Master Protocol to Assess the Safety and Recommended Phase 2 Dose of Next Generations of Autologous Enhanced NY-ESO-1/ LAGE-1a TCR Engineered T-cells, Alone or in Combination With Other Agents, in Participants With Advanced Tumors

NCTID: NCT04526509

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TITLE PAGE

Protocol Title: Master Protocol to Assess the Safety and Recommended Phase 2 Dose of Next Generations of Autologous Enhanced NY-ESO-1/ LAGE-1a TCR Engineered T cells, alone or in combination with other agents, in Participants with Advanced Tumors

Protocol Number: 209012/Amendment 04

Compound Number: GSK3901961, GSK3845097, GSK4427296

Short Title: Master Protocol of Autologous Enhanced T Cells in Advanced Tumors

Sponsor Name and Legal Registered Address:
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Regulatory Agency Identifying Number(s):

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**GSK Document Number**
Amendment 04	27 May 2022	TMF-14682560
Amendment 03	20 December 2021	TMF-14357914
Amendment 02	04 November 2021	TMF-14137790
Amendment 01	21 May 2021	TMF-13779299
Original Protocol	02 December 2019	2019N419717_00

Amendment 04 – 27 May 2022

Overall Rationale for Amendment 04:

The primary reasons for Amendment 04 are as follows:

- Changes to correct text inadvertently modified during the publication of Amendment 2. Edits in Amendment 04 reflect intended language
- Updated eligibility criteria on prior therapies across indications to incorporate standard of care practice and Investigator's discretion
- Minor changes to Substudies 1, 2, and 3 to ensure alignment of design and procedures across the 3 substudies

Section # and Name	**Description of Change**	**Brief Rationale**
Core Section		
Throughout the protocol	Made administrative changes and corrected clerical errors. Added mentions of MRCLS where missing. The designation number of the planned Long-term Follow-up Study (i.e., 208750) was added.	For clarity and consistency Update information
Section 5.2 – Participant Journey (Part 3) Section 9.10.1 – Tumor Biopsy	If it is not feasible to obtain a fresh biopsy, an archival tumor biopsy (FFPE block) taken preferably after completion of the participant's last line of therapy, preferably within 90 days prior to initiating lymphodepleting chemotherapy, may be accepted at the discretion of the Medical Monitor (or designee).	Text edited to ensure clarity

Section # and Name	Description of Change	Brief Rationale
Section 5.2 – Participant Journey (Part 4)	A sentence was added to clarify that the transfer of any individual participant to the Long-Term Follow-Up (LTFU) protocol 208750 should not exceed 6 months of completing the interventional portion of a substudy.	For clarity and to align text with Substudies' text
Section 6.3 – Rescreening/Transfer	Modified sentence to indicate that rescreening for antigen expression may not be required depending on the test platform(s) used and whether they meet study requirements	For clarity
CCI [redacted]		
Section 9.1.8 – Monitoring for Immune Effector Cell-Associated Neurotoxicity Syndrome and Section 12.7.8.2 – Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Modified existing language on Brain MRI at baseline to clarify that it should be obtained among participants with no history of CNS mestastasis if more than 3 months have elapsed between the last brain MRI and the start of lymphodepletion or if they show neurological symptoms consistent with CNS metastasis. Brain MRI at baseline should be obtained for **all** participants with a history of brain metastasis. Aligned the language between the two sections	To clarify assessment window and for safety purposes For consistency
Section 9.2.1 - Time Period and Frequency for Collecting AE and SAE Information (including Figure 4)	Text concerning the AE/SAE collection periods was modified to differentiate between the end of the interventional phase and the end of the study, and for clarity purposes.	Text edited to ensure clarity
Section 9.2.7 – Adverse Events of Special Interest (AESIs)	Split existing AESI of pancytopenia/aplastic anemia into 2 separate AESIs to avoid confusion Modified AESI of pneumonitis/pneumonia to accurately reflect intent to communicate events of pneumonitis, not pneumonia, as soon as suspected Added language to AESI of ICANS to note that events that are Grade 3 or higher should be reported as SAE within 24 hours Added language to AESI of aplastic anemia to note all events of aplastic anemia should be reported as SAE within 24 hours	To ensure clarity To align with AESI intent To align with safety monitoring intent

Section # and Name	Description of Change	Brief Rationale
Section 9.3.1 – Evaluation of Anti-Cancer Activity	Minor changes in language on acceptable imaging modalities for the study Added statement to clarify that confirmation of progression is only required in participants who are clinically stable after criteria for progression were first met	For clarity For clarity and consistency with language in Substudies 1-3
Section 9.10.1	General Guidance on Biopsies: Added language on biopsy of single measurable lesions if non-target lesions are absent or not accessible Post T-Cell Infusion Biopsies: removed "non-target lesion" to align with change above	For clarity
Section 12.3.2 – Definition of SAE	Added language to SAE definition to indicate that all events of aplastic anemia and Grade ≥3 events of ICANS or GVHD must be reported as SAEs within 24 hours	To align with Section 9.2.7
Section 12.3.5 – Reporting of SAE to GSK	Added language to SAE reporting requirements to clarify that email notifications do not replace the need for the Investigator to complete and sign the SAE CRF pages	For clarity
Section 12.5 – Appendix 5 – Genetics	Deleted mention of stool sample	Removed because sample is no longer collected, as of PA02
Section 12.6.1 – RECIST v1.1 Assessment Guidelines	Added definitions of target and non-target lesions	For clarity
Section 12.7.2.3 - Cytomegalovirus	Added language to clarify that participants will be screened for CMV IgG seropositivity at baseline, following the Schedule of Activities	For clarity

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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.

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1. SYNOPSIS

Protocol Title: Master Protocol to Assess the Safety and Recommended Phase 2 Dose of Next Generations of Autologous Enhanced NYESO-1/ LAGE-1a TCR engineered T cells, alone or in combination with other agents, in Participants with Advanced Tumors

Short Title: Master Protocol of Autologous Enhanced T Cells in Advanced Tumors

Rationale:

This master protocol will investigate a series of next generations of NY-ESO-1/LAGE-1a TCR engineered T cells that are efficacy enhanced using advances in technology, including (1) multi-component engineering (MCE, an approach in which more than one gene-product is introduced into T cells to modify the pharmacological activity of the engineered T cell), and/or (2) innovative ways of manufacturing for potentially fitter T cells. These T cells may be evaluated alone or in combination with other agents. Adoptive T-cell therapy (ACT) is a therapeutic approach that uses autologous (cancer patient's own) or allogeneic T lymphocytes obtained by leukapheresis, that are subsequently genetically engineered to express a tumor-targeting receptor, such as a T-cell receptor (TCR) or a chimeric antigen receptor (CAR), expanded *in vitro* 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 antigen (CTA) family of tumor-associated antigens. These are cytoplasmic proteins detectable in multiple cancer types including synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCLS), multiple myeloma, non-small cell lung cancer (NSCLC), bladder cancer, melanoma, gastric cancer, liver cancer, 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 157-165) 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.

GSK is currently developing an NY-ESO-1 TCR-T cell product (letetresgene autoleucel, lete-cel, GSK3377794, IND 14603 and IND 18944) that is one of the most advanced TCR-T engineered cell therapies in clinical trials for solid tumors. The retained optimized TCR clone (called NY-ESO-1^{c259} or c259) used to manufacture GSK3377794 targets the SLLMWITQC peptide bound to HLA-A*02. As of 27 January 2021, 125 patients covering six different NY-ESO-1 and/or LAGE-1a-positive malignancies have been treated with GSK3377794, with demonstration of a manageable safety profile and initial evidence of encouraging clinical activity in patients with metastatic synovial sarcoma (SS) and MRCLS. (Please refer to the most recent IB for up-to-date information regarding lete-cel). Based on this early demonstration of positive risk-benefit in SS, the FDA has granted breakthrough designation and the EMA has granted PRIME status, thus, a pivotal trial (study 208467) has been initiated with GSK3377794 (lete-cel) in SS and MRCLS. Other studies are ongoing, with early observations of clinical activity in other tumor types.

Despite the encouraging clinical activity of this first generation TCR-T, there is a need to further improve the activity and duration of response, as a proportion of patients receiving GSK3377794 (lete-cel) do not respond to treatment, and some of the patients that initially show tumor responses eventually relapse with their disease. There are several proposed mechanisms for these observations, including the immunosuppressive tumor microenvironment (TME) and limited functional activity of CD4+ T cells within the T-cell product. In order to further improve upon the clinical response rate and durability of response, next generations of engineered T-cell products are being developed that use the same affinity-enhanced TCR and in addition use (1) multi-component engineering (MCE) to incorporate within the lentiviral vector construct additional genes encoding molecules expected to enhance T-cell function and survival and/or (2) innovative ways of manufacturing for potentially fitter T cells.

Study 209012 is a master protocol to assess the initial safety, tolerability, and recommended Phase 2 dose (RP2D) of such next-generations of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other anticancer agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors.

Objectives and Endpoints:

In general, the objectives and endpoints below will apply to all substudies unless otherwise specified. Discrepancies between those stated here and those in the substudies will not require amendment and those stated in the substudies will apply.

Exploratory objectives and endpoints, if any, will be provided in the substudy specific sections.

Objectives	Endpoints
Primary	
To assess the safety, tolerability, and determine recommended phase 2 dose (RP2D) of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors	• Frequency of dose-limiting toxicities (DLTs) • Frequency and severity of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in the core protocol)
Secondary - Efficacy	
To investigate the efficacy NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors	• Overall Response Rate (ORR) (investigator assessed according to RECIST v1.1) • Duration of Response (DoR)
Secondary - Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, over time	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit

AE = adverse event; AESI = AE of special interest; DLTs = dose-limiting toxicities; DoR = duration of response; HLA = human leukocyte antigen; NY-ESO-1 = New York esophageal antigen-1; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious AE.

Overall Design:

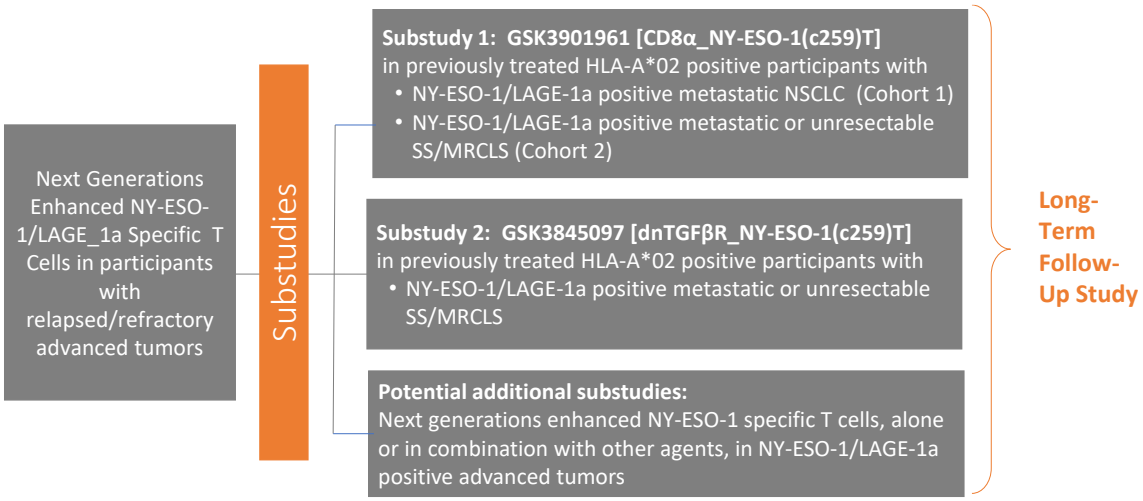
This is a master protocol investigating the safety, tolerability, RP2D and early efficacy of autologous, next-generation, NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors.

This protocol consists of a core protocol with multiple independent substudies. For further details outlining each substudy, please refer to the List of Substudies in Section 12.12.

The protocol may be amended at a later time to add additional substudies to investigate other NY-ESO-1 and/or LAGE-1a positive tumor types and other NY-ESO-1 and LAGE-1a specific T cells, potentially in combination with other agents. Details of treatment will be provided in the substudy specific sections.

Unless otherwise specified in a substudy-specific section, participants will receive NY-ESO-1 and LAGE-1a specific T cells after Screening, fulfilling eligibility criteria and completing lymphodepleting chemotherapy.

Study Schema



NOTE: Schema will not be updated for any additional substudies - please refer to Core Section 12.12 for the complete list of substudies. Participants with LAGE-1a positive tumors will be eligible if identified under a designated central laboratory test when available.

Disclosure Statement: This is an open-label treatment master protocol with no masking.

Number of Participants:

This is a master protocol consisting of multiple substudies, the overall sample size is not fixed. For details regarding planned participant numbers for each substudy, as well as for an up-to-date projected overall sample size, please refer to the List of Substudies in Section 12.12.

Any further expansion of the substudies or additional substudies will be added by amendment subject to regulatory review.

Sample size for each substudy will be documented in the substudy specific sections.

Methodology and Study Duration:

Each substudy in this Master Protocol will consist of two phases: Dose Confirmation Phase and Dose Expansion Phase.

Dose Confirmation Phase

In this phase, each next-generation NY-ESO-1/LAGE-1a specific T-cell product will be evaluated to assess/confirm the RP2D to be used in further clinical investigations.

Dose Expansion Phase

After RP2D has been determined for a given T-cell product, the dose expansion phase will begin. In this phase, additional participants will be enrolled as necessary to meet the substudy requirements for the number of evaluable participants treated at the RP2D. Each

substudy will define the maximal number of participants for this phase in the substudy specific section.

If supported by safety and efficacy results, additional participants may be enrolled to confirm the safety and efficacy in further cohort expansions via a protocol amendment. Additional details will be provided in each substudy specific section.

Participant Journey

For each individual participant, the study will consist of the following (see Figure 1 Participant Journey schema below):

Part 1: Screening

1) Target expression Screening for tumor expression of NY-ESO-1 and/or LAGE-1a. For further details regarding HLA testing, please refer to the specific substudies.

   Note: Participants screened or enrolled in other GSK studies may be considered for enrollment to this study, where it is IRB/IEC approved, on a case-by-case scenario following risk/benefit evaluation between the Investigator and Sponsor Medical Monitor (or designee).

   Where a participant was previously tested for HLA positivity and/or NY-ESO-1/LAGE-1a expression under a different GSK-sponsored protocol, retesting of HLA and/or NY-ESO-1/LAGE-1a for 209012 may not be required dependent on the test platform(s) used and whether they meet the 209012 protocol and substudy requirements. If the 209012 requirements are not met, repeat testing may be required and may or may not require new sample collection.

2) Leukapheresis eligibility screening phase to determine eligibility for undergoing leukapheresis beginning up to 28 days prior to leukapheresis.

Part 2: Leukapheresis/Manufacture

3) Leukapheresis procedure
   Note: leukapheresis may have been performed under another GSK-sponsored protocol or substudy of this protocol.

Part 3: Lymphodepletion/Treatment

4) Treatment fitness assessment and eligibility confirmation

5) Interventional phase including Lymphodepletion from Days -7 to -4, TCR engineered T-cell infusion on Day 1, and follow-up as defined in each specific substudy.
   Note: TCR engineered T cells may have been manufactured under another GSK-sponsored protocol or substudy of this protocol.

Part 4: Long-Term Follow-Up (LTFU)

6) Long-term follow-up phase for up to 15 years from the date of TCR engineered T-cell infusion.

Following **Screening** (Target Expression Screening and Leukapheresis Eligibility Screening), participants who meet substudy entry criteria will be eligible to the study. Eligible participants will undergo **Leukapheresis** to collect autologous T cells; these will undergo MCE transduction to manufacture the IP, as specified in each substudy specific section. The successful initiation of leukapheresis procedure constitutes enrollment to the study.

In order to maximize patient benefit, participants who have failed screening or withdrawn before T-cell infusion, may rescreen in the same substudy or be screened for another substudy.

Interventional Phase (Lymphodepletion/Treatment)

Once the T-cell product has been successfully manufactured, released, and is available for infusion at the site, and once participant's fitness for lymphodepletion has been assessed and additional eligibility criteria for treatment are met, participants will receive lymphodepleting chemotherapy as specified within each substudy specific section. Lymphodepleting chemotherapy may be given as outpatient treatment per institutional guidelines.

Participants will receive growth factor support with G-CSF from ~24 hours following lymphodepleting chemotherapy until neutrophil count recovery in accordance with ASCO guidelines [Smith, 2015] or institutional practice.

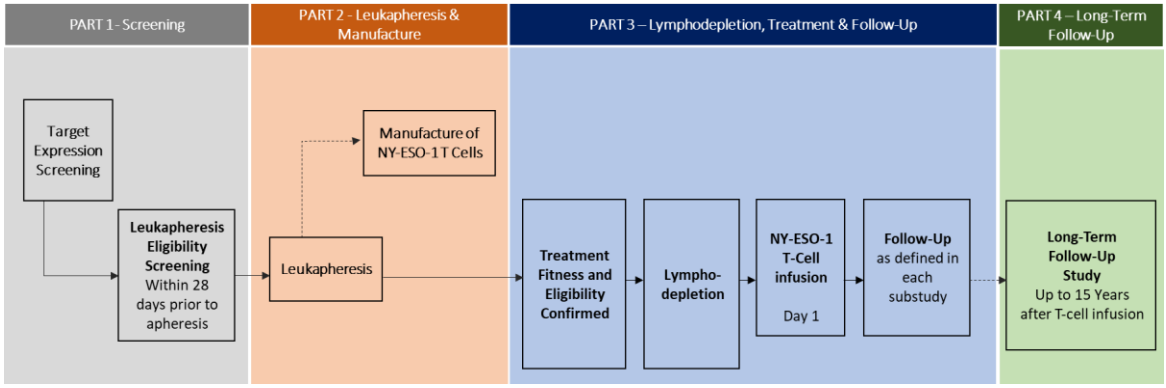
The IP will be administered as a single intravenous (IV) infusion on Day 1, unless otherwise indicated in a substudy specific section. Information on T-cell infusion, hospitalization, and follow-up guidelines is provided in the substudy specific sections.

After NY-ESO-1-specific T-cell infusion, participants are followed in the interventional portion of a given substudy until confirmed disease progression or for a minimal duration defined in each substudy specific section, at which time the participants enter the long-term follow up phase.

Long-Term Follow-Up

Upon completing the interventional portion of a given substudy, but no sooner than 90 days post T-cell infusion, participants will be entered into a separate long-term follow-up (LTFU) protocol (GSK study 208750), where they will be followed for up to 15 years after T-cell infusion for gene therapy related adverse events per health authority guidance. If LTFU protocol is not yet available at the particular clinical site, participants can be followed per LTFU schedules in substudy specific sections until LTFU protocol becomes available.

Figure 1 Participant Journey Schema



Data Monitoring Committee:

A dose selection committee (DSC) will be in place to periodically evaluate safety of the dose levels and to make dose level (de/re)-escalation decisions. The DSC will include participating investigators as well as GSK representatives from functional groups including safety, clinical, statistics and may also include external experts that are not involved in the study. Additional details on the DSC will be presented in the substudy specific sections.

2. SCHEDULE OF ACTIVITIES (SOA)

The SOA will be documented in each substudy specific section.

3. INTRODUCTION

This is a master protocol investigating the safety, tolerability, recommended Phase 2 dose (RP2D) and early efficacy of enhanced autologous NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors. This master protocol consists of a core protocol with multiple substudies.

The protocol will initially include two monotherapy substudies as described in the Study Design (Section 5). Please refer to Section 12.12 for details outlining any additional substudies.

The protocol may be amended at a later time to add additional substudies to investigate other NY-ESO-1 and/or LAGE-1a positive tumor types and other enhanced autologous NY-ESO-1 and LAGE-1a specific T cells, as monotherapy or in in combination with other anticancer agents.

3.1. Study Rationale

Adoptive T-cell therapy (ACT) is a therapeutic approach that uses autologous (cancer patient's own) or allogeneic (donor's own) T lymphocytes obtained by leukapheresis, that are subsequently genetically engineered to express a tumor-targeting receptor, such as a T-cell receptor (TCR) or a chimeric antigen receptor (CAR), expanded *in vitro* 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 antigen (CTA) family of tumor-associated antigens. These are cytoplasmic proteins detectable in multiple cancer types including non-small cell lung cancer (NSCLC), bladder cancer, melanoma, liver cancer, synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCLS), multiple myeloma 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 157-165) 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.

GSK3377794 (lete-cel) T-cell product consists of autologous T cells transduced with a self-inactivating lentiviral vector encoding an affinity-enhanced TCR (c259) targeting the SLLMWITQC peptide bound to HLA-A*02. In previous clinical trials using GSK3377794 (lete-cel), objective responses have been observed in 40 to 60% of treated participants who are HLA-A*02 positive and have NY-ESO-1^{+} SS [Robbins, 2011; Robbins, 2015; D'Angelo, 2018a]. Similar or higher response rates have been observed with this treatment in metastatic melanoma [Robbins, 2011], and multiple myeloma post autologous stem cell transplant (ASCT) [Rapoport, 2009]. GSK3377794 (lete-cel) is currently being investigated in ongoing GlaxoSmithKline (GSK) sponsored pilot clinical trials in HLA-A*02 positive participants with multiple types of tumors that are NY-ESO-1 and/or LAGE-1a positive. A summary of the clinical data obtained to date

with GSK3377794 (lete-cel) is presented in the Benefit/Risk Assessment Sections of the substudy specific sections.

Despite this encouraging clinical activity, not all patients receiving GSK3377794 (lete-cel) or other ACTs have experienced a clinical benefit. Additionally, some patients who achieved responses have eventually relapsed with their disease [**Error! Reference s ource not found.**, 2018b]. The likely mechanisms for the limited efficacy observed in some patients include the immunosuppressive effects of the tumor microenvironment (TME; e.g. by secretion of cytokines that suppress T-cell activity [Anderson, 2017]) or limited CD4+ T-cell activation, thereby limiting the persistence of infused T cells and cytotoxic activity [D'Angelo, 2018b]. Furthermore, in tumors with limited expression of the targeted antigen, the efficacy is predicted to be lower. Therefore, next generations of engineered T-cell products are being developed that use the same affinity-enhanced TCR and in addition use (1) multi-component engineering (MCE) to incorporate within the lentiviral vector construct additional genes encoding molecules expected to enhance T-cell function and survival and/or (2) innovative ways of manufacturing for potentially fitter T cells.

In this protocol, we will investigate such autologous T cells that have been genetically engineered to (a) encode the same affinity-enhanced TCR (c259) as GSK3377794 (lete-cel), and thus recognize with high affinity NY-ESO-1 and LAGE-1a tumor antigens, and at the same time (b) co-express molecules that should enhance T-cell function and survival and/or use other innovative ways of manufacturing for potentially fitter T cells. The aim of these studies will be to develop engineered T-cell products that will allow to further enhance clinical responses, with a goal to achieve long-term remissions of cancer. Given the encouraging early clinical activity of GSK3377794 (lete-cel), and in consideration of additional potential advantages provided by MCE, a clinical investigation of the next-generation products is justified to achieve maximum efficacy across NY-ESO-1 and /or LAGE-1a expressing tumors.

3.2. Background

3.2.1. Adoptive cell therapies and NY-ESO-1/LAGE-1a

Genetic modification of autologous T cells targeting specific tumor antigens has been developed to overcome immune tolerance and to empower the immune system of the cancer patient with lasting anti-tumor immunity permitting long term remission of disease. The TCR approach to engineered T-cell therapy is attractive because TCRs can recognize not only cell surface proteins (as is the case with CAR T cells) but also any intracellular proteins, since TCRs recognize peptide fragments of these intracellular proteins that are processed and presented on the cell surface in the context of HLA. The TCR-modified T-cell approach is also particularly suited for solid tumors due to their ability to recognize low concentrations of these intracellular cognate antigens. In addition, the TCR approach mimics the natural function of the T cell by recruiting the endogenous signalling molecules and adhering to correct spatial orientation between the T cell and its target. These aspects may contribute to a manageable safety profile, high anti-tumor activity and enhanced persistence of the infused TCR engineered T cells, providing ongoing anti-cancer protection.

Morgan et al. first demonstrated tumor regression in 2 of 17 patients after adoptive transfer of genetically engineered T cells expressing a TCR specific for a melanocyte-differentiating antigen (MART-1) [Morgan, 2006]. Responding patients demonstrated long term persistence of infused T cells. Identification and sequencing of TCRs able to recognize epitopes expressed by human tumors together with improvements in TCR gene transfer technology has allowed for rapid redirection of T cells and targeting of a variety of tumor antigens, including gp100, carcinoembryonic antigen (CEA) [Johnson, 2009], p53 [Kuball, 2005], cancer testis antigen (CTA) family members such as NY-ESO-1 [Robbins, 2011] as well as melanoma associated antigens (MAGE)-A3 [Morgan, 2013], MAGE-A4 [Kageyama, 2015] and MAGE-A10 [Border, 2018].

Studies conducted by the NCI Surgery Branch have demonstrated that adoptive immunotherapy using T cells genetically engineered to recognize NY-ESO-1 following lymphodepletion led to objective antitumor responses in 4 of 6 patients (67%) [Robbins, 2011] and 11 of 18 patients (61%) [Robbins, 2015] with SS. The estimated overall 3- and 5-year survival rates for patients with SS were 38% and 14%, respectively [Robbins, 2015]. No toxicity attributed to the modified cells was reported in these studies.

Most clinical protocols with TCR gene therapy have incorporated preconditioning of the patient with a lymphodepleting chemotherapy regimen prior to T-cell infusion [Rohaan, 2019]. Lymphodepletion prior to ACT may enhance immune reconstitution by the transferred cells and increase tumor-specific responses. Immune reconstitution is enhanced through homeostatic mechanisms that facilitate expansion of T lymphocytes [Baccala, 2005], facilitate trafficking of the engineered T cells [Pinthus, 2004], and also improve the persistence of infused T cells. Lymphodepletion can also enhance 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 release of inflammatory cytokines and induction of tumor apoptosis with resulting cross presentation of tumor antigens to T cells. Therefore, a lymphodepleting regimen containing cyclophosphamide and fludarabine will be used in this study; details will be provided in the substudy specific sections.

GSK is currently developing a therapy consisting of autologous CD4+ and CD8+ T cells expressing the affinity-enhanced NY-ESO-1^{c259} TCR (GSK3377794, lete-cel), that is capable of recognizing the SLLMWITQC peptide, which is derived from CTA family members NY-ESO-1 and LAGE-1a, upon presentation on HLA-A*02:01, *02:05 or *02:06. GSK3377794 has been infused into more than 125 patients with various malignancies. Treatment with GSK3377794 has demonstrated unprecedented clinical responses in patients with SS, inducing a clinical response in 50% of treated SS patients with a manageable safety profile [D'Angelo, 2018b]. This therapy is currently being explored in other tumors including NSCLC, Myxoid round cell liposarcoma (MRCLS), and multiple myeloma. Details are provided in Section 3.2.2.

3.2.2. GSK3377794 (letetresgene autoleucel, lete-cel)

All next-generation T-cell therapies anticipated to be tested in this master protocol encode the same affinity-enhanced TCR (c259) as GSK3377794 (lete-cel), and thus recognize NY-ESO-1 and LAGE-1a tumor antigens with high affinity. Therefore, prior

observations and outcomes of clinical trials investigating GSK3377794 (lete-cel) provide relevant information for the development of these next-generation therapies.

As of 27 January 2021, 125 participants have received GSK3377794 infusions in clinical studies. For the most up to date information regarding lete-cel, please refer to the current IB. The clinical development program for GSK3377794 consists of 11 studies in 6 tumor types, including the studies that were started by Adaptimmune and taken over by GSK and studies started by GSK since the transfer. An observational long-term follow-up study 208750 is also being conducted in participants exposed to GSK adoptive cell therapies in a previous clinical trial.

Additional information about GSK3377794 (lete-cel), including a review of existing data in the context of the benefit/risk assessment of the next-generation products, is provided in the relevant substudy specific sections.

3.2.3. Next Generation Engineering

Despite the encouraging early efficacy results, not all patients receiving GSK3377794 have experienced a clinical benefit. Additionally, some patients who achieved responses have eventually relapsed with their disease [D'Angelo, 2018b].

Enhanced efficacy of tumor-specific T cells against solid tumors, aiming to increase the response rate of TCR T-cell therapy, requires strategies levering their immunosuppressive microenvironment. Therefore, GSK has been developing enhancement technologies and the first wave of these enhancements includes using MCE to enable co-expression of additional components alongside the NY-ESO-1^{c259} TCR. The first two assets to be investigated are GSK3901961 and GSK3845097 as described in Substudy 1 and Substudy 2. Other NY-ESO-1 specific T cells may be introduced into this protocol and will be described in additional substudy specific modules. For more details regarding additional substudies, please refer to the List of Substudies in Section 12.12.

4. OBJECTIVES AND ENDPOINTS

In general, the objectives and endpoints below will apply to all substudies unless otherwise specified. Discrepancies between those stated here and those in the substudy specific sections will not require amendment and those stated in the substudy specific sections will apply.

Exploratory objectives and endpoints, if any, will be provided in the substudy specific sections.

Objectives	Endpoints
Primary	
To assess the safety, tolerability and determine recommended phase 2 dose (RP2D) of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors	• Frequency of dose-limiting toxicities (DLTs) • Frequency and severity of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in the core protocol)
Secondary – Efficacy	
To investigate the efficacy of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors	• Overall Response Rate (ORR) (investigator assessed according to RECIST v1.1) • Duration of Response (DoR)
Secondary – Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, over time	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit

AE = adverse event; AESI = AE of special interest; DLTs = dose-limiting toxicities; DoR = duration of response; HLA = human leukocyte antigen; NY-ESO-1 = New York esophageal antigen-1; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious AE.

5. STUDY DESIGN

5.1. Overall Design

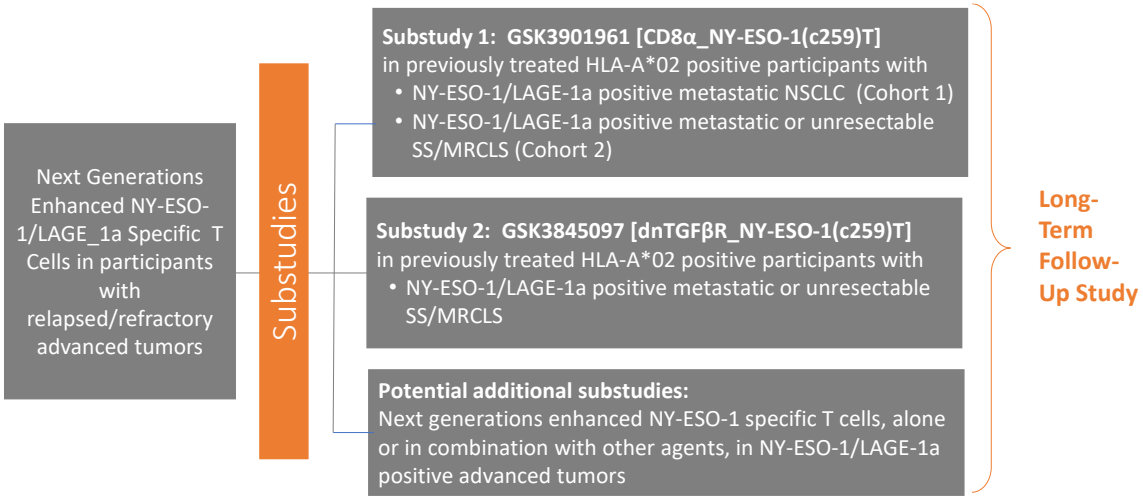
This is a master protocol investigating the safety, tolerability, RP2D and early efficacy of autologous, next-generation, NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors.

This protocol consists of a core protocol with multiple independent substudies. The protocol will initially include two substudies to investigate (a) GSK3901961 (NY-ESO-1 TCR engineered T cells co-expressing the α-chain of the CD8 co-receptor) in previously treated (2L+) HLA-A*02^{+} participants with NY-ESO-1^{+} advanced SS, MRCLS, or NSCLC (Substudy 1) and (b) GSK3845097 (NY-ESO-1 TCR engineered T cells co-expressing, the dnTGF-βRII receptor) in previously treated (2L+) HLA-A*02^{+} participants with NY-ESO-1^{+} advanced SS or MRCLS (Substudy 2). For more details regarding additional substudies and indications, please refer to the list in Section 12.12.

The protocol may be amended at a later time to add additional substudies to investigate other NY-ESO-1 and/or LAGE-1a positive tumor types and other NY-ESO-1 and LAGE-1a specific T cells, potentially in combination with other agents (see Figure 2 Study Design schematic below). Details of treatment are provided in the substudy specific sections.

Unless otherwise specified in a substudy specific section, participants will receive NY-ESO-1 and LAGE-1a specific T-cells after Screening, fulfilling eligibility criteria and completing lymphodepleting chemotherapy.

Figure 2 Study Design



Note: Schema will not be updated for any additional substudies - please refer to Core Section 12.12. for the complete list of substudies. Participants with LAGE-1a positive tumors will be eligible if identified under a designated central laboratory test when available.

Participants included in different substudies may have the same eligibility criteria.

Sponsor will inform Investigators of the participant assignments between substudies and indicate if the participant is to receive a split dose as a sentinel participant (see Section 8.1.2 for details) and the number of remaining slots.

Each substudy in this Master Protocol will consist of two phases: Dose Confirmation Phase and Dose Expansion Phase.

5.1.1. Dose Confirmation Phase

In this phase, each next-generation NY-ESO-1 and LAGE-1a T-cell product will be evaluated to assess/confirm the RP2D to be used in further clinical investigations.

5.1.2. Dose Expansion Phase

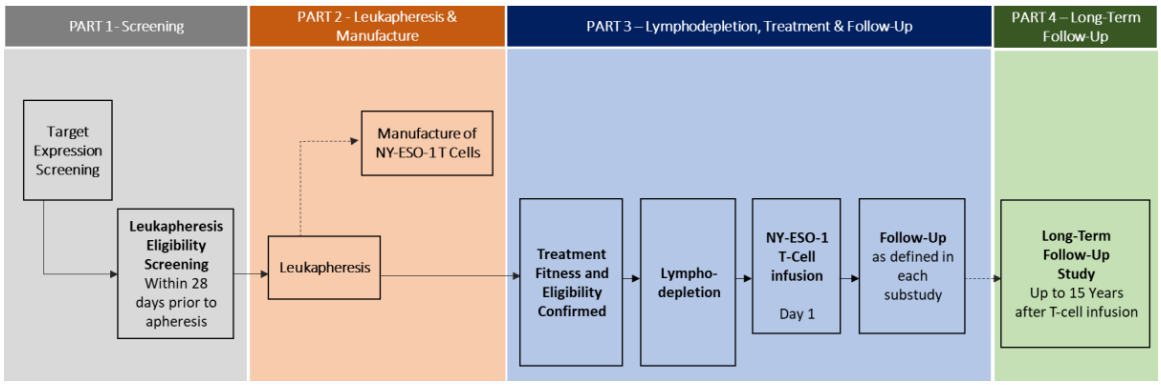
After RP2D has been determined for a given T-cell product, the dose expansion phase will begin. In this phase, additional participants will be enrolled as necessary to meet the substudy requirements for the number of evaluable participants treated at the RP2D. Each substudy will define the maximal number of participants for this phase in the substudy specific section.

If supported by safety and efficacy results, additional participants may be enrolled to confirm the safety and efficacy in further cohort expansions via a protocol amendment. Additional details will be provided in each substudy specific section.

5.2. Participant Journey

Unless otherwise specified in a given substudy specific section, participants will undergo stepwise enrolment followed by treatment according to defined phases within each substudy (See Patient Journey Schema Figure 3).

Figure 3 Patient Journey Schema



Part 1: Screening

1) Target expression Screening for tumor expression of NY-ESO-1 and/or LAGE-1a. For further details regarding HLA testing, please refer to the specific substudies.

   Note: Participants screened or enrolled in other GSK treatment studies may be considered for enrollment to this study, where it is IRB/IEC approved, on a case-by-case scenario following risk/benefit evaluation between the Investigator and Sponsor Medical Monitor (or designee).

   Where a participant was previously tested for HLA positivity, and/or NY-ESO-1/LAGE-1a expression under a different GSK-sponsored protocol, testing of HLA and/or NY-ESO-1/LAGE-1a for 209012 may not be required dependent on the test platform(s) used and whether they meet the 209012 protocol requirements. If the 209012 requirements are not met, repeat testing may be required and may or may not require new sample collection.

2) Leukapheresis screening phase to determine eligibility for undergoing leukapheresis beginning up to 28 days prior to leukapheresis.

Part 2: Leukapheresis/Manufacture

3) Leukapheresis procedure
   Note: leukapheresis may have been performed under another GSK-sponsored protocol or substudy of this protocol.

Part 3: Lymphodepletion, Treatment, and Follow-up

4) Treatment fitness assessment and eligibility confirmation,

5) Interventional phase including Lymphodepletion from Days -7 to -4, TCR engineered T-cell infusion on Day 1, and follow-up as defined in each specific substudy.
   Note: TCR engineered T cells may have been manufactured under another GSK-sponsored protocol or substudy of this protocol.

Part 4: Long-Term Follow-Up (LTFU)

6) Long-term follow-up phase for up to 15 years from the date of TCR engineered T-cell infusion.

Part 1: Screening

Screening will consist of two phases: Target Expression Screening and Leukapheresis eligibility Screening.

Participant Target Expression Screening may start at any time after diagnosis of advanced disease; either prior to or during ongoing line of prior therapy, subject to any substudy specific requirements; also consult the substudy requirements for specific mandates on the presence of radiographic and/or clinical disease progression at the time of Screening. Once informed consent has been obtained, a blood sample will be collected from each participant for testing the presence of HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06. NY-ESO-1 and/or LAGE-1a expression will also be evaluated on representative tumor tissue from a formalin-fixed and paraffin-embedded (FFPE) archival (most recent preferred) or fresh biopsy. HLA-typing and tumor antigen expression testing should be performed sequentially (considering the expected >50% attrition with HLA) but may also be performed in parallel at the discretion of the Investigator. If an Investigator is aware of a participant's positive HLA status (the presence of HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 based on high resolution local testing), the Investigator may provide tumor tissue for antigen testing either at the same time as or before a confirmatory HLA test by the central laboratory. Participants with the HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 alleles and whose tumor expresses

the NYESO-1 and/or LAGE1a antigen, as measured using validated testing at a designated central laboratory, are eligible to undergo further Screening under this protocol. Note: target expression Screening may also be performed under a separate Screening protocol such as the GSK molecular disease characterization initiative (MDCI) study (213299), or another GSK-sponsored NY-ESO-1 and/or LAGE-1a targeting T-cell protocol or substudy of this protocol.

Once participants are deemed HLA positive and tumor antigen expression positive, they will sign the main study informed consent to undergo screening for leukapheresis eligibility within 28 days prior to the day of the scheduled leukapheresis procedure.

Part 2: Leukapheresis/Manufacture

Following completion of Screening, participants who meet substudy entry criteria will be eligible to the study. Eligible participants will undergo leukapheresis to collect autologous T cells.

The initiation of leukapheresis procedure constitutes enrollment to the study.

The collected T cells will undergo MCE transduction to manufacture the investigational product (IP), as specified in each substudy specific section.

Unless otherwise specified in a substudy specific section, bridging therapies (e.g., chemotherapy, local therapy [e.g. radiotherapy, cryoablation, surgical resection]) may be administered between leukapheresis and the start of lymphodepletion, if a participant cannot be treatment-free. The following conditions must be met:

1. Mandatory washout periods prior to start of T-cell infusion must be respected (see substudy specific sections)
   AND
2. Indicated based on benefit/risk assessment and/or local regulatory requirements and following agreement with Sponsor's Medical Monitor (or designee)
   AND
3. Treatments, AEs and other clinical observations are reported into the current study database

Participants who failed screening or withdrew before T-cell infusion, may rescreen in the same substudy or consider entering screening for another substudy (see Section 6.3 for further details).

Part 3: Lymphodepletion, Treatment, and Follow-up

The following conditions need to be satisfied prior to initiating lymphodepletion and T-cell treatment:

1. Treatment fitness assessment and confirmation of additional inclusion/exclusion criteria for treatment must be completed from 1 to 10 days prior to initiating lymphodepleting chemotherapy.
2. Baseline radiological tumor assessment is obtained from 1 to 10 days prior to lymphodepletion.
3. T cell product availability verified by site for each criterion below:

a. Confirmation of successful manufacture of T-cell product
b. T-cell product satisfies all release criteria as stated on Certificate of Analysis
c. T-cell product available for infusion at the site per criteria specified in the Drug Product and Infusion Manual

4. Pre-treatment tumor biopsy collected within 28 days prior to initiating lymphodepletion is required. This biopsy will be used as the Baseline sample for CCI analyses. If it is not feasible to obtain a fresh biopsy, an archival tumor biopsy (FFPE block) taken preferably after completion of the participant's last line of therapy, preferably within 90 days prior to initiating lymphodepleting chemotherapy, may be accepted at the discretion of the Medical Monitor (or designee). For participants who already provided a fresh biopsy for antigen expression and did not receive any subsequent bridging or standard of care line of anti cancer therapy, this screening biopsy may be used as the Baseline sample provided the screening biopsy was taken preferably within 90 days prior to initiating lymphodepleting chemotherapy.

Following lymphodepletion, after ~24 hours of completing lymphodepleting chemotherapy, participants must receive Granulocyte-Colony Stimulating Factor (G-CSF) support. The formulation of G-CSF to be used can be decided by the Investigator based on the institutional practice.

Refer to substudy specific sections for information on T-cell infusion, hospitalization and follow-up guidelines. Additional close monitoring or hospitalization may be warranted based upon clinical need and is at Investigator's discretion (please refer to Section 9.1 for safety assessments and monitoring; Section 9.2 for reporting of adverse events; and Section 12.7 for supportive care guidance on T-cell infusion, CRS and other potential risks).

If additional treatments are combined with T-cell treatment in future substudies, the details of those treatments will be given in the substudy specific sections.

Participants will be frequently monitored for any unexpected Grade ≥3 AE and any SAEs, according to the SoA in the substudy specific sections.

Participants who are not eligible for study intervention by the time T Cells expire, will be withdrawn from the study and will not undergo lymphodepletion within this study.

Any remaining manufactured T cells from each participant (whether or not eligible for study intervention) will be stored by the Sponsor for the current shelf life of the cells after manufacture is completed. After expiry of the shelf life, the stored T cells can be destroyed or, if consented by the participant, used for scientific research at the Sponsor's discretion for a period of up to 15 years depending on local regulations.

Part 4: Long-Term Follow-Up (LTFU)

Upon completing the interventional portion of a given substudy (as defined for each substudy specific section), but no sooner than 90 days post T-cell infusion (in order to capture enough safety information), participants will be entered into a separate long-term

follow-up (LTFU) protocol (GSK Study 208750) and will be monitored for 15 years. If the LTFU protocol is not yet available at the particular clinical site, participants can be followed per LTFU schedules in substudy specific sections until the LTFU protocol becomes available. The transfer of any participant to the LTFU study (Study 208750) should occur within 6 months of completing the interventional portion of a substudy.

5.3. Number of Participants

This is a master protocol consisting of multiple substudies, the overall sample size is not fixed. For details regarding participant numbers for each substudy, please refer to the List of Substudies in Section 12.12.

Any further expansions of individual substudies or additional new substudies will be added via protocol amendments with specification of number of participants for each expansion and/or substudy. Any additional sub-studies will be added by amendment subject to regulatory review.

Refer to the substudy specific sections for additional details on sample size determinations.

5.4. Scientific Rationale for Protocol Design

This is a master protocol to assess, via multiple independent substudies, the safety, tolerability and RP2D of multiple autologous next-generation NYESO-1 and/or LAGE1a specific T cells, alone or in combination with other agents, in HLA-A*02 positive participants with NYESO-1 and/or LAGE1a positive advanced tumors. GSK seeks to test these next-generation agents in the clinic, relying on the currently available nonclinical models and the first-generation GSK3377794 (lete-cel) clinical and nonclinical data, with an optimal strategy to enable rapid establishment of tolerability and proof of concept for efficient further development decisions and early access to patients.

This master protocol design provides the flexibility to conduct multiple substudies, thereby permitting an efficient evaluation of agents in multiple indications compared with separate clinical trials (either by indication or by product). This mechanism provides an opportunity to optimize the choice of candidates to advance into mid/late-stage product development by permitting efficient generation of clinical data that cannot be gained using currently available nonclinical models [FOCR, 2019].

The scientific rationale for the design of each substudy, including rationales for the participant population and dose selection, are provided in each substudy specific section.

5.4.1. Data Monitoring Committee

A dose selection committee (DSC) will be in place (see substudy specific sections for descriptions) to periodically evaluate safety of the dose levels and to make dose level (de/re)-escalation decisions. Further details on the DSC will be provided in the Dose Selection Plan. Further data review committees may be put in place as cohort expansions and new substudies may require it.

5.5. End of Study Definition

5.5.1. End of Study for Individual Participants

Refer to the substudy specific sections for end of substudy definitions for individual participants.

5.5.2. End of Master Protocol

This Master Protocol will end as of the last visit of the last participant in the last substudy, or when all participants have met their respective substudy end criteria including those who have died, withdrawn consent, are lost to follow-up, or have transferred to the separate long-term follow up protocol (GSK study 208750) for observation of delayed AEs and survival for a duration of 15 years post-T-cell infusion in accordance with Food and Drug Administration (FDA) [FDA, 2020b] and European Medicines Agency (EMA) guidance [EMA, 2009].

6. PROTOCOL POPULATION

The protocol will enroll participants with advanced tumors to independent substudies.

Initially, the protocol will enroll participants with advanced SS or MRCLS (Substudies 1 and 2) and advanced NSCLC (Substudy 1). Any additional substudy may include SS, MRCLS, NSCLC or other tumor types – please refer to Core Section 12.12 for the complete list of substudies. The rationale for the chosen tumor settings will be discussed in the substudy specific sections.

The full detailed inclusion and exclusion criteria and lifestyle considerations are presented in the substudy specific section. Prospective approval of protocol deviations relating to enrolment criteria for the purpose of recruiting participants, also known as protocol waivers or exemptions, is not permitted.

6.1. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical protocol but are not subsequently enrolled into a substudy. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, disease characteristics, prior line of anti-cancer treatments and any serious adverse events (SAEs).

6.2. Screening under Other GSK Studies

Participants screened or enrolled in other GSK treatment studies may be considered for enrollment to this study, where it is IRB/IEC approved, on a case-by-case scenario following risk/benefit evaluation between the Investigator and Sponsor Medical Monitor (or designee).

Where a participant was previously tested for HLA and/or NYESO1/LAGE-1a expression under a different GSK-sponsored protocol, testing of HLA and/or NYESO1/LAGE-1a for 209012 may not be required dependent on the test platform(s) used and whether they meet the 209012 protocol requirements. If the 209012 requirements are not met, repeat testing may be required and may or may not require new sample collection. Other screening/baseline assessments or procedures (e.g., biopsy collection, imaging) performed under a separate GSK sponsored protocol may be accepted, in consultation with the Sponsor Medical Monitor.

6.3. Rescreening/Transfer

Individuals who do not meet the criteria for participation in a given substudy at any stage (screen failure for reasons other than HLA negative and/or NY-ESO-1 and LAGE-1a negative diagnostic status) or who were withdrawn prior to T-cell administration may be rescreened or transferred to any applicable GSK-sponsored study or substudy of this protocol. HLA typing may not need to be repeated (Section 6.2). Rescreening for the

NY-ESO-1 and/or LAGE-1a antigen expression of a recent tumor sample may not be required depending on the test platform(s) used and whether they meet the 209012 protocol requirements (Section 6.2). For participants who were withdrawn after leukapheresis but before T-cell administration and for whom suitable leukapheresis or manufactured product is available, the requirement for leukapheresis and/or remanufacture may be waived after consultation with the Sponsor.

7. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Details of study interventions and guidelines, including dose, administration, and concomitant medications are specified in each substudy specific section.

In general, however, study intervention will follow the steps outlined in Section 5.2 of the Core Protocol and in the intervention schema included there.

8. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The guidelines and criteria below apply to all protocol participants except where otherwise indicated in substudy specific sections.

8.1. Discontinuation of Study Intervention

8.1.1. Single Dose Administration

As the T-cell intervention is expected to be administered as a single dose for all autologous next-generation NY-ESO-1 and LAGE-1a specific T cells to be tested in this master protocol, there is no possibility of discontinuation of study intervention. In the event of severe reactions during infusion, the infusion may be interrupted.

Please refer to the current Drug Product and Infusion Manual for details of dose administration. Please refer to Section 9.1 for safety assessments and monitoring; Section 9.2 for reporting of adverse events; and Section 12.7 for supportive care guidance on T-cell infusion, CRS and other potential risks.

Infusion-related reactions Grade 3 or higher during infusion should be reported to Sponsor promptly :

- GSK CGT Patient Supply Co-ordinator by e-mail (GSK.CELL@gsk.com) or by phone +1-833-GSK-CELL (+1 833-475-2355) or +44 800-026-6295 (for European countries);
- Medical Monitor or designee (contact information provided in SRM).

In participants with infusion-related reaction Grade ≤2, infusion may be restarted once resolved to Grade <1. The bag of cells that was being infused prior to reaction, cannot be used beyond 45 minutes after thawing.

Should other agents be added in future either as monotherapy or combination therapy, any additional details will be added via amendment to this core or via additional substudies, as applicable.

8.1.2. Split Dose Administration

While dosing is described in Section 8.1.1, please refer to each substudy for substudy-specific details outlining if there is a requirement for the T cells to be administered as split dosing (i.e., in two aliquots) to the first (‘sentinel’) participant; such split dosing may be extended to additional participants based on the safety and tolerability profile. Split dosing may also be required in other substudies if appropriate. Additionally, future next-generation NY-ESO-1 and LAGE-1a specific T cells may be administered by repeat dosing, or as single doses as well as in combination with other agents administered by repeat dosing.

As such, individual stopping rules described below apply only to those participants receiving multiple administrations of the T cells and/or other anticancer agents used in combination.

For such participants:

- The subsequent dose of the agent will be administered as described in the respective substudy specific section, unless one of the following events occurs:
  - Clinical deterioration that in the opinion of the Investigator in consultation with the Sponsor warrants interrupting or stopping the dosing;
  - Unacceptable toxicity, whether meeting the definition of DLT or not, and including meeting the standard GSK stopping criteria for liver chemistry and QTc prolongation (see below);
  - Death;
  - Any other substudy-specific event requiring IP interruption or discontinuation;
- Even if the dosing was interrupted or stopped for any of the reasons above, participants will continue to be followed according to the SOA, as discontinuation of dosing does not represent withdrawal from the study.

In the event of severe reactions during the T-cell infusion, the infusion may be interrupted.

8.2. Dose Limiting Toxicity

The toxicities listed below are considered to be dose limiting toxicities (DLTs) if:

- They are considered at least possibly related to transduced T cells; AND
- They occur within the DLT-assessment period of 28 days after the initial dosing of T cells. For participants receiving T cells as split dose, DLT assessment period will begin at the start of the first infusion and continue for 28 days after completion of the last infusion.

Of Note:

- Toxicities related to lymphodepletion will be evaluated by the Sponsor and DSC on a case-by-case basis.
- Attribution of relatedness to treatment for DLT will be discussed between the Investigator, the Sponsor, DSC, and any other substudy-specific review committee; where attribution varies, the most conservative assessment will be retained.
- Additional toxicities which occur following the DLT assessment period of 28 days may be declared DLTs, after consultation between the Sponsor, DSC, and any other substudy-specific review committee based on the emerging safety profile.

- Individual substudies may expand the list below to include additional defined DLTs as appropriate based on the mechanism of action of the specific transduced T cells.

The following will be considered DLTs:

1. Grade 4 or greater toxicities (including death), that are at least possibly related to the investigational agent.
2. Grade 3 toxicities that are at least possibly related to the investigational agent and do not resolve to Grade ≤1 (or Baseline) within 7 days from the onset of the event.
3. CTCAE Grade ≥3 non-infectious pneumonitis not responding to oxygen supplementation and systemic steroid treatment.
4. Any Grade 3 cytokine release syndrome (CRS) at least possibly related to study agent that does not improve to Grade <2 toxicity within 7 days with or without dexamethasone 10 mg q12hr IV (or an equivalent corticosteroid dose).
5. Any Grade 4 CRS at least possibly related to study product that does not improve to Grade ≤2 (or Baseline) within 7 days.
6. Any Grade 3 or greater neurotoxicity that does not resolve to Grade ≤2 within 72 hours.
7. Any Grade ≥3 organ toxicity (exclusive of CRS toxicity) involving major organ systems that persists for >72 hours and occurs within 28 days of infusion.

The following constitutes exceptions from DLTs:

- Laboratory abnormalities CTCAE Grade 3 or 4 not considered clinically significant by the investigator
- Electrolyte abnormalities CTCAE Grade 3 or 4 responding to best supportive care per institutional guidelines
- Hypoalbuminemia CTCAE Grade 3 or 4 responding to best supportive care per institutional guidelines
- Fever and chills CTCAE Grade 3 or 4 clinically stable with best supportive care per institutional guidelines
- AE related to the cancer or its progression
- Thrombocytopenia CTCAE Grade 3 or 4 not associated with significant bleeding
- Anemia CTCAE Grade 3 or 4 responding to best supportive care per institutional guidelines
- Lymphocytopenia CTCAE Grade 3 or 4
- Leukopenia CTCAE Grade 3 or 4

For any additional DLT criteria based on asset, please refer to the substudy.

8.2.1. Liver Chemistry Stopping and Increased Monitoring Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

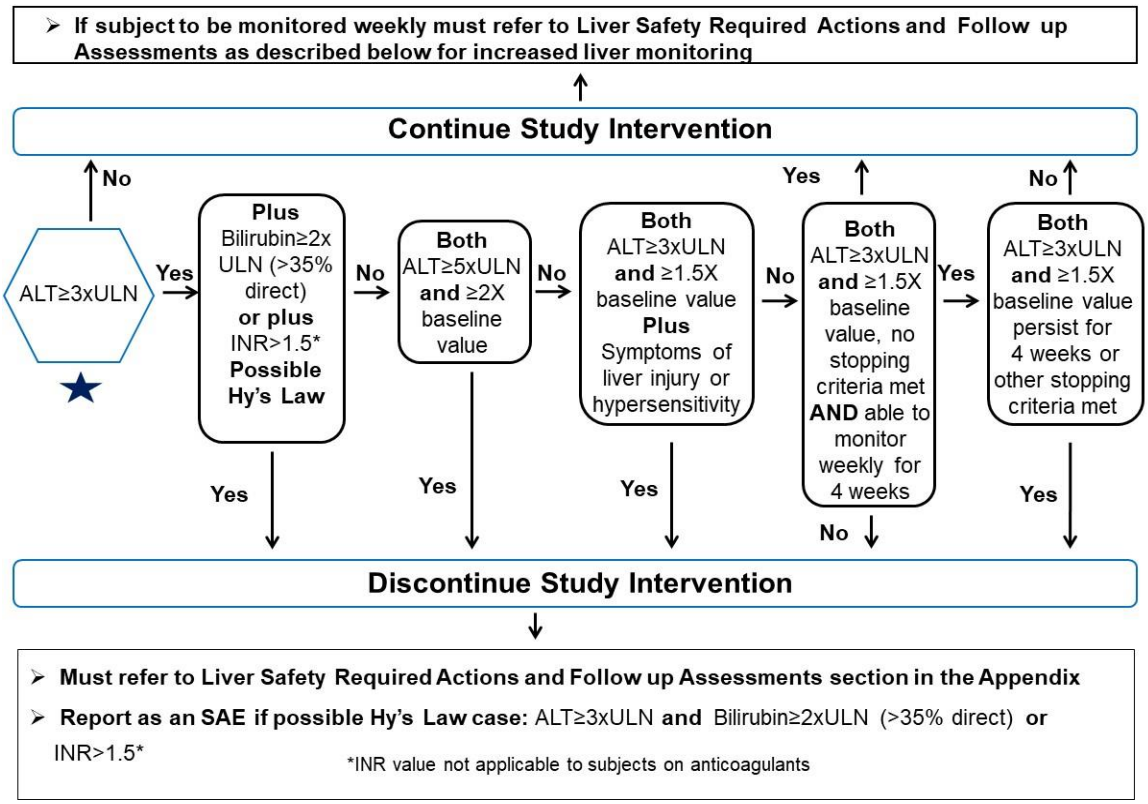
8.2.1.1. Stopping Criteria

The next dose or the second aliquot of a split dose will not be administered to a participant if:

- A participant meets one of the conditions outlined in the algorithm below

OR

- When in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.



The following Level 1 and Level 2 monitoring are required for all participants.

8.2.1.2. Level 1 Monitoring

In the event that a participant develops elevations in liver function test (LFT) parameter values 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 and ≥1.5x Baseline value **but** ALT <5x ULN and <2x Baseline value **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, stabilise or return to within Baseline • If, during monitoring, ALT increases to ≥5xULN and ≥2x Baseline value or remains ≥3x ULN and ≥1.5x Baseline value 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.

ALT = alanine aminotransferase; ULN = upper limit of normal; AST = aspartate aminotransferase.

8.2.1.3. Level 2 Monitoring

In the event that the participant 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	**Both** ALT ≥5xULN **and** ≥2x Baseline value
ALT Increase	**Both** ALT ≥3xULN **and** ≥1.5x Baseline value 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 1.5x Baseline value 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 liver event 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) **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow-up assessments within **24 hrs**	• 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

• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within Baseline (pre-gene therapy) • A specialist or hepatology consultation is recommended **For all other criteria:** • 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)	• 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 **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRFs.

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.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CRF = Case Report Form; LDH = lactate dehydrogenase; INR = International normalized ratio; ULN = upper limit of normal.

8.2.1.4. Administration of Subsequent T Cell Dose(s) after Liver Stopping Criteria Met

If participant meets liver chemistry stopping criteria and subsequently the liver event resolves, any planned subsequent T cell dose(s) may be administered, provided:

- GSK Medical Governance approval **is granted**
- Ethics and/or Institutional review board (IRB) approval is obtained, if required, and
- Separate consent for intervention restart/rechallenge is signed by the participant

If GSK Medical Governance approval to administer subsequent dose(s) **is not granted**, then participant will continue in the study for protocol-specified follow up assessments.

8.2.2. QTc Stopping Criteria

The following QTc stopping criteria will apply:

- QTc >500 msec

OR

- Change from Baseline of QTc >60 msec

For participants with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

Notes:

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from further study treatment. This formula may not be changed or substituted once the participant has been enrolled.
  - For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
  - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety electrocardiograms (ECGs) and other non-protocol specified ECGs are an exception.
- The QTc should be based on the average of triplicate ECG readings obtained over a brief (e.g., 5-10 minute) recording period.

8.2.3. Temporary Discontinuation

Infusion of the IP can be stopped for any adverse events experienced by the participant or observed by the treating physician. Refer to the Drug Product and Infusion Manual for details of dose administration.

NY-ESO-1 specific TCR engineered T cells intervention is typically administered as a single dose via IV infusion, except for sentinel participants who will receive a split dose (Section 8.1.2). In the event of severe reactions associated with liver toxicities during or in between the 2 doses, the infusion may be interrupted or delayed. Please refer to Section 8.1 for guidance on discontinuation of intervention and restarting of infusion.

Should other agents be added in future either as monotherapy or combination therapy, any additional details will be added via amendment to this core or via additional substudies, as applicable.

8.3. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the substudy to which he/she is enrolled at any time at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons. No further assessments will be required, and the Investigator must document this in the site study records.
- Treatment follow-up may be permanently discontinued for any of the following reasons:
  - Significant deviation(s) from the protocol

  - Withdrawal of consent by participant (or proxy)
  - Participant is lost to follow-up
  - Closure or termination of the study by the sponsor

- Participants for whom treatment follow-up has been permanently discontinued will continue into the LTFU phase of the protocol or, if consent was given, into the LTFU study GSK 208750.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the substudy to which he/she is enrolled after providing study samples, GSK will retain those samples and any results generated from testing prior to participant withdrawal, as described in the informed consent. If the participant specifically requested destruction of their samples at the time of withdrawal, the Investigator should notify GSK, and document this in the site study records. Once notified, GSK will not perform any further testing, and will destroy the sample.
- A participant will be considered to have withdrawn from the substudy to which he/she is enrolled if the participant has not died and is lost to follow-up (Section 8.4 of the core protocol).
- Refer to the SoA in each substudy specific section for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.

8.4. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the substudy to which he/she is enrolled.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the substudy to which he/she is enrolled.

Discontinuation of specific sites or of the study as a whole is handled as part of Section 12.1.

8.5. Study Stopping and Pausing Rules

The study will pause enrolment and stop treatment for all participants if any of the following events occur pending submission to Regulatory Agencies and review by any substudy-specific safety review committees (e.g., DSC), IRBs/ECs, and the Sponsor.

- Uncontrolled clonal T-cell proliferation felt to be attributable to the next-generation NY-ESO-1 and LAGE-1a specific T cells
- A case of documented symptomatic progressive cerebral edema confirmed by an expert neurological examination and computed tomography (CT)/ magnetic resonance imaging (MRI), that is not responding to treatment.
- A biologically functional positive Replication Competent Lentivirus (RCL) after 2 confirmed positive tests by polymerase chain reaction (PCR).
- Death directly attributed to the investigational agent by the Investigator and DSC.
- Any event of Guillain-Barre syndrome (GBS) as diagnosed by a neurologist according to diagnostic guidance for GBS [Fokke, 2014].

Premature termination of individual substudies or the entire study may occur if:

- Sponsor, in consultation with any safety review committees (e.g., DSC), decides for any reason that participant safety may be compromised by continuing the study.
- The Sponsor decides to discontinue the development of the intervention to be used in this study.

It is expected that AEs will occur frequently in these patient populations based on the underlying advanced malignancies in the initial and future substudies and these can be SAEs. A review of individual significant safety events across all substudies in conjunction with the cumulative review of safety data by the sponsor, any substudy-specific safety review committees (e.g., DSC), and Investigators, will inform decisions for premature termination of individual substudies or the entire study. SAEs that are related to the direct effects of T-cell therapy may be considered as stopping criteria. Interruption or premature termination of individual substudies or the entire clinical study may also occur because of a regulatory authority decision.

Please refer to specific substudies for any additional substudy-specific assessments.

9. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures and their timings are summarized in the SoA tables within each substudy specific section.

Unless otherwise stated in a substudy specific section and its SoA, the descriptions and guidelines in this section and subsections will apply. Where there is a discrepancy between this core protocol and the relevant substudy specific section, the substudy specific section should be followed.

Adherence to the substudy design requirements, including those specified in the SoA, is essential and required for study conduct. Protocol waivers or exemptions are not allowed except for immediate safety concerns.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Informed consent must be signed by a participant before any study required procedures are performed. However, procedures conducted as part of the routine clinical management (e.g., imaging studies) and conducted prior to signing of the study informed consent may be used for Screening/Baseline assessments provided the procedure fulfills the protocol defined specifications and has been performed within the protocol indicated timeframe.

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

1. 12-lead ECG
2. Vital signs
3. Blood draws

9.1. Safety Assessments

Please refer to the individual substudies for any additional substudy-specific monitoring.

9.1.1. Dose Selection Committee

Dose selection committee (DSC) will be established for making dose recommendations for each investigational agent, i.e. substudy, based on a review of all relevant data. The DSC will include participating investigators as well as GSK representatives from functional groups including safety, clinical, statistics and may also include external experts that are not involved in the study. The committee(s) will be tasked to determine

whether the same dose can be given to additional participants; or decide to move to a lower dose level for any of the investigational agents as guided by the appropriate statistical model (described in the substudy specific section). The membership, meeting structure and frequency, data to be reviewed, and recommendations to be made by the committee will be described in the Dose Selection Plan.

9.1.2. GSK Safety Review Team

For substudies where a DSC is not implemented or once DSC is no longer required when dose confirmation phase has completed for a particular substudy, an internal GSK Safety review team will be put in place, consisting of a cross functional team of the appropriate disciplines required to ensure holistic evaluation of the safety profile of the T-cell product under evaluation. The Safety review team will conduct systematic, periodic and documented reviews of available safety data and address the safety issues pertinent to the medicine.

9.1.3. Physical Examinations

A complete physical examination will include, at a minimum, weight and assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height will be assessed at timepoints indicated in the SoA in each substudy specific section.

A dedicated physical examination will include assessments based on specific concerns of the Investigator.

Investigators should pay special attention to clinical signs related to previous serious illnesses or tumor sites.

9.1.4. ECOG Performance Status

The performance status will be assessed using Eastern Cooperative Oncology Group (ECOG) scale (Section 12.8) at the time points specified in the SoA in each substudy specific section.

9.1.5. Vital Signs

Blood pressure, pulse measurements (rate and oximetry), respiratory rate, and body temperature should be assessed per institutional standards. The same methods should be used throughout the course of the study. Manual techniques will be used only if an automated device is not available.

Where vital signs and blood collection for laboratory tests are performed on the same day, vital signs should be taken before blood collection for laboratory tests.

9.1.6. Cardiac Assessments

All cardiac assessments will be performed locally at the site.

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

An echocardiography (ECHO) or multigated acquisition scan (MUGA) scan is required to determine eligibility. Additional scans may be performed as clinically indicated. NOTE: the same method of cardiac evaluation should be used consistently for all follow-up scans.

Single or triplicate 12-lead ECG (as indicated in the SOA) will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT intervals corrected for heart rate by Fridericia's formula (QTcF) or QT duration corrected for heart rate by Bazzetts's formula (QTcB) intervals. The replicate ECG tracings should be obtained as closely as possible in succession. The full set of triplicates should be completed within approximately 4 minutes.

Serum troponin and NT-proBNP / BNP as markers for cardiac health will be assessed prior to initiation of lymphodepletion.

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 Tcell 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 T-cell infusion will be monitored through proactive pharmacovigilance to determine causality. Supportive treatment for these participants will be provided per standard clinical practice guidelines.

9.1.7. 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 for 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.

9.1.8. Monitoring for Immune Effector Cell-Associated Neurotoxicity Syndrome

Brain MRI (or CT scan if an MRI is not feasible) must be obtained for all participants as part of leukapheresis eligibility Screening. This should be repeated at Baseline prior to lymphodepletion in the following:

- All participants with a history of CNS metastasis, and
- Participants with no history of brain metastasis if more than 3 months have elapsed between the last brain MRI and the start of lymphodepletion or if they show neurological symptoms consistent with CNS metastasis.

Brain MRI may be performed as clinically indicated thereafter.

Immune Effector Cell-Associated Encephalopathy (ICE) (see Section 12.7.8 for definition) must be measured immediately prior to T-cell infusion on the day of infusion, and then according to each substudy SoA. Participants with known brain metastases must be monitored at least twice per day for the first 5 days following T-cell infusion. If a participant is found to have Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), the ICE neurological assessment tool should be used at least twice per day until ICANS is resolved or stable and may be measured at follow up visits if indicated.

For management of ICANS, refer to Section 12.7.8.

9.1.9. Monitoring 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 according to diagnostic guidance for GBS [Fokke, 2014] to provide expert recommendations to guide appropriate diagnostic workup such as electromyography (EMG), lumbar puncture, infectious panel to guide management and follow up (See Section 12.7.10).

Any additional monitoring requirements or modifications to these requirements as well as any management guidelines will be addressed in the substudy specific sections.

9.1.10. Clinical Safety Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All abnormal laboratory values considered clinically significant occurring during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or Baseline. If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 12.2 must be conducted in accordance with the laboratory manual and the SoA in each substudy specific section. Reference ranges for all safety parameters must be provided to the site by the laboratory responsible for the assessments.

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[redacted]

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[redacted]

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[redacted]

9.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 12.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The Investigator or designee is responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention or the study.

In the absence of a clear alternative etiology (e.g., chemotherapy, concomitant medications, disease progression, infections, etc.), AEs should be considered potentially immune-related. Immune-related AEs may include diarrhea/colitis, rash, hepatitis, Graft versus host disease (GVHD), cytokine release syndrome (CRS), secondary pancytopenia, pneumonitis, endocrinopathies, nephritis, and any other manifestations that may indicate an immune-related phenomenon.

Adverse events of special interest (AESIs) in this study are defined in Section 9.2.7. They need to be reported to Sponsor (Medical Monitor or designee) **within 24 hours via e-mail** (see SRM for further instructions).

Certain events in this protocol are identified as delayed AEs and **should be marked** as delayed AEs **in the eCRF**.

Delayed AEs are defined as those events that fall into one or more of the 6 categories listed below and which occur either after disease progression or last Interventional Phase visit, whichever occurs first. Delayed AEs will be collected as part of the LTFU phase of the substudy or in the LTFU Study 208750, contingent upon formal transfer of participant to Study 208750.

Delayed AEs will be collected until 5 years have elapsed from last T-cell infusion, or until patient dies, withdraws consent or is deemed lost to follow-up. Delayed AEs will be recorded in the CRF if reported by the patient or investigator between years 6 – 15. Any AE collected on-study may also be indicated as a delayed AE by the Investigator at their discretion.

The 6 categories for delayed AEs are as follows:

- 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 hematologic disorder
- New incidence of an infection (potentially related to gene modified cell therapy)
- Unanticipated illness or hospitalization deemed related to gene modified cell therapy

Time period for designating an event from the above categories as delayed AE in the eCRF will be provided in the SRM. If a participant is monitored in this protocol post disease progression (i.e., for LTFU phase), the only AEs that will be assessed are delayed AEs.

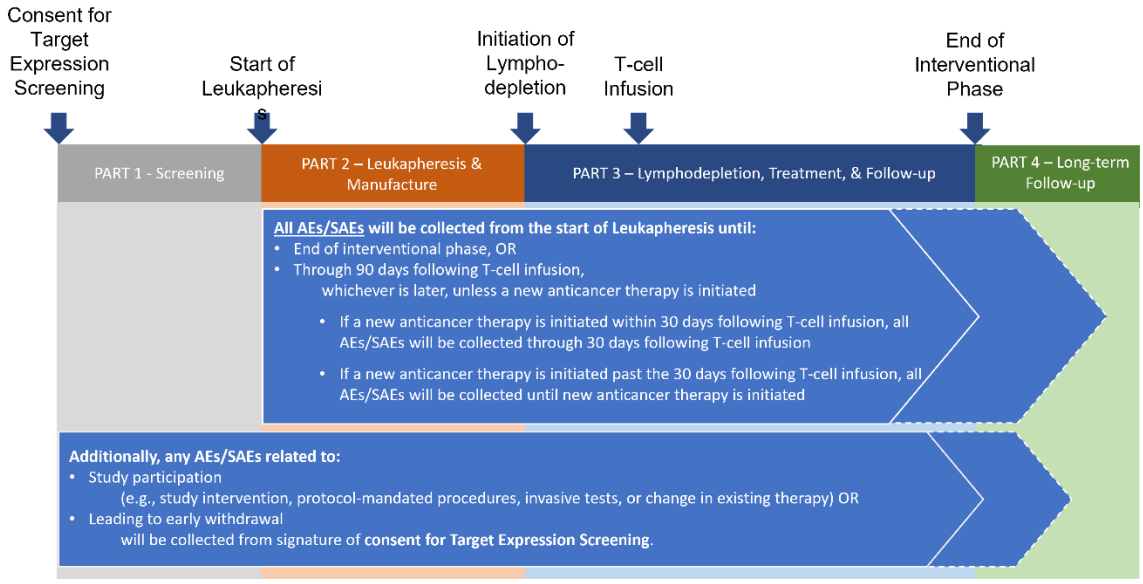
9.2.1. Time Period and Frequency for Collecting AE and SAE Information

Collection of AEs and SAEs starts from the timing of signing the ICF for target expression screening, and will be performed as follows:

- All AEs/SAEs will be collected from the start of leukapheresis until the end of the interventional phase, or through 90 days following T-cell infusion, whichever is later, unless a new anticancer therapy is initiated.
  - If the new anticancer therapy is initated within 30 days following T-cell infusion, AEs/SAEs will be collected through 30 days following T-cell infusion.
  - If the new anticancer therapy is initated beyond the 30 days following T-cell infusion, AEs/SAEs will be collected until the new anticancer therapy is initiated.
- Additionally, any AEs or SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or leading to early withdrawal will be collected in the AE section of the CRF from the time a participant signs the informed consent for target expression Screening. All other relevant events that begin before the start of leukapheresis but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

Figure 4 displays the AE/SAE collection time periods in relationship to the 4 phases of a substudy intervention.

Figure 4 Time Period for Collecting AE and SAE Information



- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 12.3. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Events of special interest (AESIs) (Section 9.2.7) will be reported to the Sponsor (Medical Monitor or designee) within 24 hours via e-mail (see SRM for further instructions): AESIs should be communicated as soon as suspected, and any confirmed diagnosis must be reported immediately.
- Events occurring after the end of the interventional phase and before the participant enrolls onto the LTFU Study 208750 will be collected and reported as indicated in the SoA for Part 4 in each substudy specific section.
- Events occurring after the participant enrolls onto the LTFU Study 208750 will be collected and reported in the LTFU protocol database.
- Any SAE, including death, brought to the attention of an Investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be related to investigational product.

9.2.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.3.

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2.7), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Section 12.3.

In all cases of SAE that occur after T-cell infusion, a transgene copy (persistence) sample must be obtained if feasible.

9.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

- Should female participant or female partner of male participant become pregnant, collect details of pregnancy and report per guidelines in Section 12.4.
- The Investigator should inform GSK within 24 hours of learning of any pregnancy and should follow the procedures outlined in Section 12.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.
- If appropriate, the investigator should advise fertile male participants to consider collecting and storing viable sperm prior to undergoing lymphodepletion, given that cyclophosphamide may result in partial (oligospermia) or total (azoospermia) sterility.

9.2.5. Cardiovascular Events and Death

For any cardiovascular events detailed in Section 12.3.3 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 cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical dictionary 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.

9.2.6. Progression of Underlying Malignancy

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

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

9.2.7. Adverse Events of Special Interest (AESIs)

Adverse events of special interest for this trial should be communicated to Sponsor (Medical Monitor or designee) as soon as suspected, and any confirmed diagnosis must be reported to GSK within 24 hours via email to the Sponsor (Medical Monitor or designee) (see SRM for further instructions). The AESIs for this study are as follows:

- Cytokine release syndrome [Note: Grade 3 or higher should be reported as SAE within 24 hours.]
- Graft vs host disease [Note: Grade 3 or higher should be reported as an SAE within 24 hours.]
- Immune Effector Cell-Associated Neurotoxicity Syndrome Grade 1 persisting beyond 24 hrs or associated with concurrent CRS; or Grade 2 or higher [Note: Grade 3 or higher should be reported as SAE within 24 hours.]
- Guillain Barre syndrome including acute inflammatory demyelinating polyneuropathy (AIDP) [Note: All cases must be reported as SAEs within 24 hours.]
- Pancytopenia with at least 1 cell line Grade ≥3, present on or after Day 28 after the T-cell infusion
- Aplastic anemia [Note: All cases must be reported as SAEs within 24 hours.]
- Pneumonitis
- Neutropenia Grade 4 lasting ≥28 days

Additional AESI that does not need to be reported within 24 hours is:

- Treatment-related inflammatory response at tumor site(s)

Each substudy specific section may define additional AESIs. For any additional substudy-specific AESIs, refer to the substudy (see Section 12.12 for a list of the substudies).

9.3. Efficacy Assessments

See substudy specific sections for any additional assessments.

9.3.1. Evaluation of Anti-Cancer Activity

Tumor assessments for response and progression will be evaluated according to RECIST v1.1 [Eisenhauer, 2009] and iRECIST (see Section 12.6):

- RECIST v1.1 will be used in the assessment of disease burden (target and non-target lesions determination) at Baseline and as the primary measure of tumor response endpoints.
- CCI [redacted]

See the SoA within each substudy specific section for the schedule of assessments of anti-cancer activity. Acceptable imaging modalities for this study include:

- IV (iodine based) contrast enhanced CT scan +/- oral contrast of the chest and abdomen/pelvis (CT is the preferred modality for tumor assessments). Extremities and/or skin lesions will be assessed if required.
- In cases where contrast enhanced CT is contraindicated:
    - For the abdomen/pelvis, a MRI (with and without gadolinium contrast) is acceptable;
    - For the chest, a non-contrast enhanced CT or a MRI (with and without gadolinium contrast) is acceptable.
- MRI of the extremities or brain with and without gadolinium contrast, or per site standard of care if contraindicated.
- Digital photographs of skin lesions including a ruler for estimating the size of the lesion.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. FDG-PET/CT will be collected centrally if performed as part of the site's routine disease management, at Screening and whilst on study.

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

Tumor measurements for each participant should be performed by the same Investigator or radiologist (to the extent that this is feasible).

To allow time for the immune response to become apparent and for potential transient inflammatory reaction of the disease to the treatment ('tumor flare'), response will not be assessed before 4 weeks post infusion of the next-generation NY-ESO-1 and LAGE-1a specific T cells, unless there is unequivocal clinical evidence of deterioration. Response or progression is to be confirmed by repeat imaging scan performed not earlier than 4 weeks and not later than 8 weeks after the criteria for response or progression were first met (confirmation of progression is only required in participants who are clinically stable after criteria for progression were first met). For post-Baseline assessments, a window is permitted to allow for flexible scheduling as defined in the SoA within each substudy specific section.

Tumor images will be obtained by the site and transmitted to a central imaging vendor for potential central review. The process for tumor imaging and transmission to the central imaging vendor are detailed in the Imaging Manual.

9.3.2. Long-Term Follow-up

Upon the end of the applicable substudy for each participant, they will be entered into a separate LTFU protocol (GSK study 208750) and will be monitored for up to 15 years post T-cell infusion for observation of delayed AEs (defined in Section 8.3) in accordance with FDA requirements for gene therapy clinical trials [FDA, 2020b; FDA, 2010]. If the LTFU protocol is not yet available at the particular clinical site, participants can be followed per LTFU schedule under this protocol (See SOAs in substudy specific sections) until the LTFU protocol becomes available.

9.4. Patient Reported Outcomes

Patient reported outcomes may be assessed in some of the substudies. If patient reported outcomes are included, specifics regarding these measures will be outlined in the substudy specific sections.

9.5. Treatment of Overdose

Next-generation NY-ESO-1 and LAGE-1a specific T cells must be administered as specified in the substudy specific section by trained personnel at the investigational sites in this study. Infusion guidelines provided in the Drug Product and Infusion Manual must be strictly followed, including dosing amounts, premedication, duration of infusion, and vital sign monitoring.

In the event of an allergic reaction, the infusion must be immediately stopped, and anti-histamine treatment initiated. Please refer to Section 12.7 for further supportive care guidance. Acute mild respiratory distress developing during or immediately after (within 48 hours) T-cell infusion can be managed with supportive care, as detailed in Section 12.7.

Should any substudy of the protocol include agents other than the T cells, any additional overdose considerations will be provided in the applicable substudy specific section.

9.6. Pharmacokinetics

Pharmacokinetics of T cells (also known as T-cell expansion or persistence) in the peripheral blood will be measured in the participants to establish the relationship between T-cell expansion and response to IP. Persistence of T cells is also monitored as a long-term safety measure.

Whole blood samples of approximately 8 mL will be collected for measurement of transduced cell quantities as described in the SOA; samples will be processed to PBMC. DNA will be isolated from these PBMCs to quantify the transduced cells using PCR of the Psi transgene as described in Section 9.1.12. Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The following PK parameters will be computed, as data permit:

- Cmax: maximum concentration/T-cell expansion
- Tmax, time of Cmax
- AUC(0-t), area under the concentration/T-cell expansion time curve from 0 to time t.

Samples collected for analyses of transduced T Cells in blood may also be used to evaluate safety or efficacy aspects that may arise during or after the study.

9.7. Pharmacodynamics

Serum cytokine levels and other[redacted] measured for research purposes (see Section 9.10) may be evaluated for pharmacodynamic relationships with investigational agent administration.

9.8. Genetics

Genetics research may be conducted on a genetics blood sample, plasma, and on tumor samples collected in the study as indicated in Section 9.10. Consent for Leukapheresis and Treatment encompasses consent for genetics research.

See Section 12.5 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Study reference manual (SRM) or Laboratory Manual.

9.9. Immunogenicity Assessments

Serum samples for determination of antibodies against NY-ESO-1 specific (c259) T cells will be taken from all participants for anti-drug antibody (ADA) testing.

Serum samples will be tested for antibodies against NY-ESO-1 (c259) specific T cells using a validated assay and a tiered-testing scheme (e.g., Screening, confirmation, and titer assays). Briefly, all samples will be tested in a Screening assay to identify potential positives. Next, all potentially positive samples will be tested in a confirmation assay to determine the specificity of the response. Finally, titer values will be determined for all confirmed positive samples. For each participant, immunogenicity results (e.g., positive or negative) and titer values will be reported. Other analyses (e.g., neutralizing antibody assay) may be performed to further characterize the antibodies, if necessary.

All samples collected for detection of antibodies to study intervention(s) may also be evaluated to enable interpretation of the antibody data.

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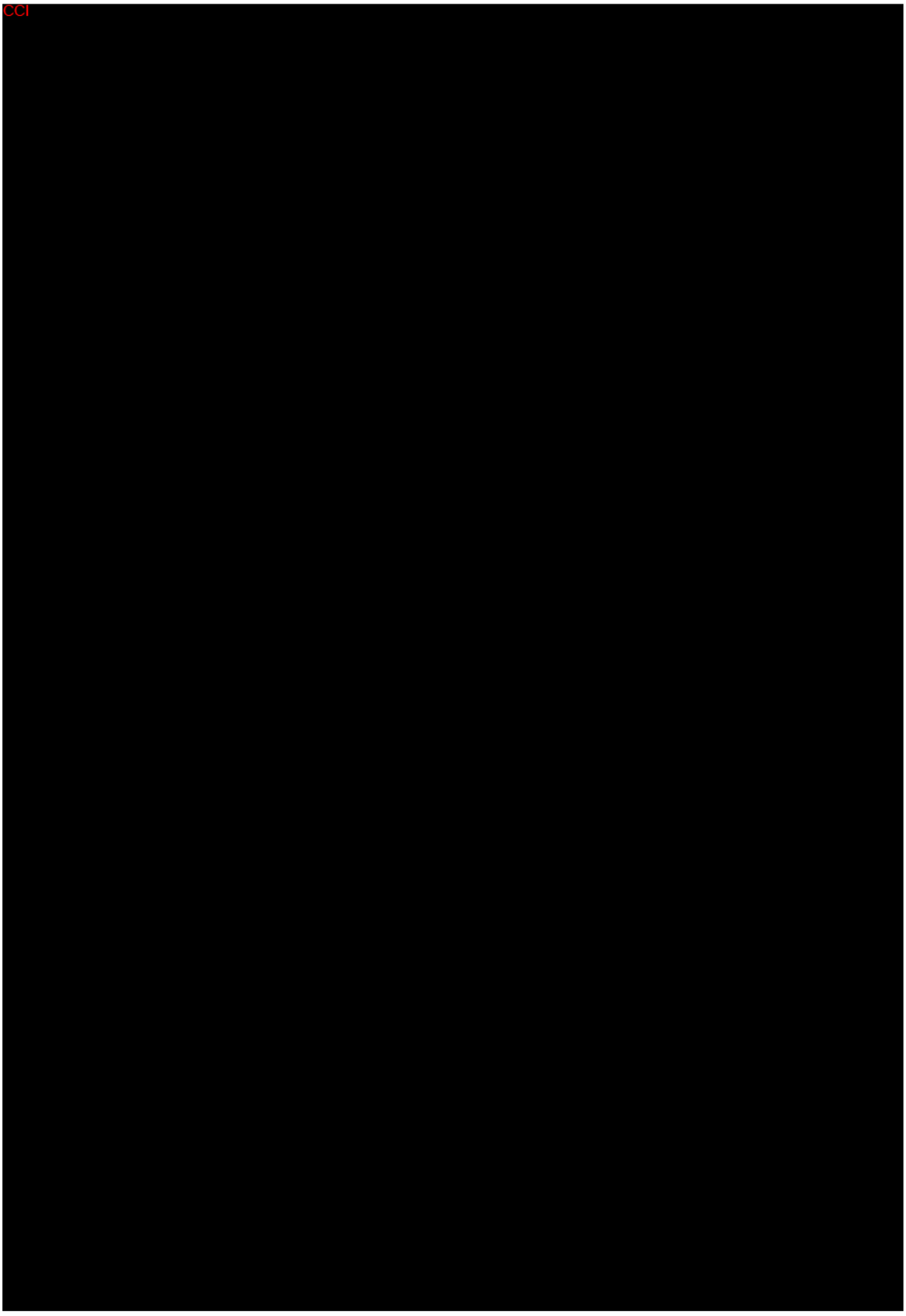

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9.11. Request for Autopsy in case of Death Following Administration of Gene Transfer Agents

In accordance with the FDA guidance [FDA, 2020a], autopsies will be requested of the families for all participants who die due to an adverse event potentially or directly related to the T-cell infusion. To assure compliance, guidelines for performing an autopsy are provided in the SRM.

10. STATISTICAL CONSIDERATIONS

Each substudy will be analysed and reported separately.

The following statistical considerations apply to all substudies. Substudy specific considerations are detailed in the individual substudy specific section.

10.1. Statistical Hypotheses

The primary and secondary objectives of this study are described overall in Section 4 and detailed in the individual substudy specific sections.

Hypotheses for individual substudies are detailed in the substudy specific sections.

All analyses will be descriptive.

10.2. Sample Size Determination

Sample size determination is detailed separately for each substudy.

10.3. Data Analysis Considerations

Data will be listed and summarized according to GSK reporting standards, where applicable. Complete details will be documented in the Statistical Analysis Plan (SAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final study report.

Other data analysis considerations are detailed in the substudy specific sections.

10.4. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened Population	All participants who signed an ICF to participate in the study.
Enrolled Population	All participants who started leukapheresis procedure.
Intent-To-Treat (ITT) Population	All participants who started leukapheresis procedure.
Modified ITT (mITT) Population	All participants who received any dose of NY-ESO-1 specific T cells.
Evaluable Population	All participants who received T--cell infusion and completed at least 2 disease assessments after infusion or progressed or died or were withdrawn or lost to follow-up from the substudy

10.5. Statistical Analyses

10.5.1. Interim Analyses

Interim analyses are detailed separately for each substudy.

10.5.2. Key Elements of Analysis Plan

10.5.2.1. Safety Analyses

All safety analyses will be performed on the ITT and mITT Populations.

Endpoint	Statistical Analysis Methods
Primary	DLTs/AEs/SAEs/AESIs will be summarized using frequencies and proportions.

Safety data will be presented in tabular and/or graphical format and summarized descriptively by dose and study cohort. No formal analysis will be conducted comparing substudies or cohorts.

All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the SAP.

Extent of Exposure

The number of subjects administered study treatment will be summarized.

Adverse Events

Adverse events will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0.

Events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study intervention. In addition, AEs, if listed in the NCI-CTCAE v5.0, will be summarized by the maximum grade.

Characteristics (e.g., number of occurrences, action taken, grade) of the AEs of special interest (specified in Section 9.2.7) will be summarized separately.

The incidence of deaths and the primary cause of death will be summarized.

Dose-limiting toxicities (DLTs, specified in Section 8.2) will be listed for each subject and summarized by dose cohort according to International Data Standards Library (IDSL) standards.

Clinical Laboratory Evaluations

Haematology and clinical chemistry data will be summarized using frequencies and proportions according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the SAP.

Other Safety Measures

Data for vital signs, ECGs, and ECHOs will be summarized based on predetermined criteria identified to be of potential clinical concern (PCI). Further details will be provided in the SAP.

10.5.2.2. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Secondary	Overall response rate (ORR), which includes confirmed complete or partial response as determined by investigator assessment per RECIST 1.1 will be reported along with Clopper-Pearson exact 95% CI. Duration of response (DOR) will be summarized using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant. Maximum expansion/persistence (Cmax), time to Cmax (Tmax), and area under the time curve from zero to time t AUC(0-t) will be presented in tabular or graphical form, if data permit.

Secondary Efficacy Endpoints

ORR: Overall response rate is defined as the percentage of participants with a confirmed CR or a confirmed PR relative to the total number of participants within the analysis population at any time per RECIST v1.1 as determined by the local investigators.

ORR will be reported in the ITT and mITT populations by cohort at the time of primary analysis.

Participants with unknown or missing response will be treated as non-responders, i.e., these participants will be included in the denominator when calculating the percentage. The number and types of responses, as defined by RECIST v1.1, will be listed and summarized separately, as appropriate.

The observed confirmed ORR will be reported by cohort at the primary analysis along with 95% Clopper-Pearson exact confidence interval (CI).

DOR: Duration of response (DOR) is defined as, in the subset of participants who show a confirmed CR or PR as assessed by local investigators, the time from first documented evidence of CR or PR until the first documented sign of disease progression or death. Duration of response will be summarized descriptively, if data warrant, using Kaplan-Meier medians and quartiles. Details on rules for censoring will be provided in the SAP.

Response assessment and DOR will be listed for participants in the mITT population.

11. REFERENCES

Anderson KG, Stromnes IM, Greenberg PD. Obstacles posed by the tumor microenvironment to T cell activity: A case for synergistic therapies. *A Cancer Cell*. 2017; 31:311-325.

Baccala R, Gonzalez-Quintial R, Dummer W, et al. Tumor immunity via homeostatic T cell proliferation: mechanistic aspects and clinical perspectives. *Springer Semin Immunopathol*. 2005; 27: 75-85.

Border EC, Sanderson JP, Weissensteiner T et al. Affinity-enhanced T-cell receptors for adoptive T-cell therapy targeting MAGE-A10: strategy for selection of an optimal candidate. *Oncoimmunology*. 2018;8:e1532759.

D'Angelo SP, Druta M, Liebner DA et al. Pilot study of NY-ESO-1^{c259} T cells in advanced myxoid/round cell liposarcoma. *J Clin Onc* 2018a; 36 suppl: 3005-3005.

D'Angelo SP, Melchiori L, Merchant MS et al. Antitumor Activity Associated with Prolonged Persistence of Adoptively Transferred NY-ESO-1 (c259)T Cells in Synovial Sarcoma. *Cancer Discov*. 2018b; 8:944-957.

Davila ML, Riviere I, Wang X et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med*. 2014;6:224ra2.

Dignan FL, Clark A, Amrolia P et al. Diagnosis and Management of acute graft-versus-host disease. *Br J Haematol*. 2012;158:30-45.

Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

EMA Guideline on Follow-Up of Patients Administered with Gene Therapy Medical Products (October 2009).

FDA (2020a). Guidance for Industry, Long Term Follow-Up After Administration Of Human Gene Therapy Products (January 2020).

FDA (2020b) Guidance for Industry, Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up (January 2020).

FDA Briefing Document – Testing for Replication Competent Retrovirus (RCR)/Lentivirus (RCL) in RCR/RCL based gene therapy products (November 2010).

Fidler C, Klumpp T, Mangan K at al. Spontaneous graft versus host disease occurring in a patient with multiple myeloma after autologous stem cell transplant. *Am J Hematol*. 2012;87:2-21.

Fokke C, van den Berg B, Drenthen J et al. Diagnosis of Guillain-Barre´ syndrome and validation of Brighton criteria. *Brain*. 2014;137:33-43.

Friends of Cancer Research (FOCR), Designing the Future of Cell Therapies. White Paper (2019).

Garfall A, Kalos M, Furth EE et al. Autologous aGVHD associated with infusion of T cells with engineered specificity for NY-ESO-1 and LAGE-1 following high-dose melphalan and ASCT in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:S134.

Glucksberg H, Storb R, Fefer A et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A- matched sibling donors. *Transplantation*. 1974; 18:295–304.

Johnson LA, Morgan RA, Dudley ME et al. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. *Blood*. 2009; 114:535-546.

Kageyama S, Ikeda H, Miyahara Y Imai N et al. Adoptive transfer of MAGE-A4 T-cell receptor gene-transduced lymphocytes in patients with recurrent esophageal cancer. *Clin Cancer Res*. 2015; 21:2268-2277.

Kaufman RM, Djulbegovic B, Gernsheimer T et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2015; 162:205-213.

Kline J, Subbiah S, Lazarus HM et al. Autologous graft-versus-host disease: harnessing anti-tumor immunity through impaired self-tolerance. *Bone Marrow Transplant*. 2008; 41:505-513.

Kuball J, Schmitz FW, Voss RH et al. Cooperation of human tumor-reactive CD4(+) and CD8(+) T cells after redirection of their specificity by a high-affinity p53A2.1-specific TCR. *Immunity*. 2005; 22:117–129.

Lee DW, Gardner R, Porter DL et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014; 124:188-195.

Lee DW, Santomasso BD, Locke FL et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Manilla P, Rebello T, Afable C et al. Regulatory Considerations for Novel Gene Therapy Products: A Review of the Process Leading to the First Clinical Lentiviral Vector. *Human Gene Therapy*. 2005; 16:17–25.

Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. *Journal for ImmunoTherapy of Cancer* 2020;8:e001511.

Miller AD. Retrovirus packaging cells. *Human Gene Therapy*. 1990; 1:5-14.

Morgan RA, Chinnasamy N, Abate-Daga D, et al. Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy. *J Immunother*. 2013;36:133-151.

Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science*. 2006; 314:126-129.

Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T cell therapy-assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018; 15:47-62.

Pinthus JH, Waks T, Malina V, et al. Adoptive immunotherapy of prostate cancer bone lesions using redirected effector lymphocytes. *J Clin Invest*. 2004; 114:1774-1781.

Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. *N Engl J Med*. 2019; 380:1726-1737.

Rapoport AP, Stadtmauer EA, Aqui N, et al. Rapid immune recovery and graft-versus-host disease-like engraftment syndrome following adoptive transfer of costimulated autologous T cells. *Clin Cancer Res*. 2009; 15:4499-4507.

Robbins PF, Kassim SH, Tran TL, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1–Reactive T cell receptor: long-term follow-up and correlates with response. *Clin Cancer Res*. 2015;21:1019-1027.

Robbins PF, Morgan RA, Feldman SA, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. *J Clin Oncol*. 2011; 29: 917-924.

Rohaan MW, Wilgenhof S and Haanen JBHG. Adoptive cellular therapies: the current landscape. *Virchows Arch*. 2019; 474:449-461.

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncology*. 2017;18:143-152.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American society of clinical oncology clinical practice guideline update. *J Clin Oncol*. 2015; 33:3199-3212.

Tocilizumab SmPC 2020. https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf

Tocilizumab USPI 2020. https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/2e5365ff-cb2a-4b16-b2c7-e35c6bf2de13/spl-doc?hl=tocilizumab

Van Koningsveld R, Steyerberg EW, Hughes RA, et al. A clinical prognostic scoring system for Guillain-Barré syndrome. *Lancet Neurol*. 2007 Jul;6(7):589-94.

Walgaard C, Lingsma HF, Ruts L, et al. Early recognition of poor prognosis in Guillain-Barre syndrome. *Neurology*. 2011; 76:968-975.

Walgaard C, Lingsma HF, Ruts L, et al. Prediction of Respiratory Insufficiency in Guillain-Barre´ Syndrome. *Ann Neurol*. 2010; 67:781–787.

Willison HJ, Jacobs BC, van Doom PA. Guillain-Barre Syndrome. *Lancet*. 2016; 388:717-727.

Wolf AM, Wolf D, Steurer M, et al. Increase of regulatory T cells in the peripheral blood of cancer patients. *Clin Cancer Res*. 2003;9:606-12.

12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

12.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.1.2. Financial Disclosure

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

12.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

12.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Publication Policy
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the

sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

12.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

12.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including

handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 30 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

12.1.8. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development.

12.1.9. Remote Monitoring and Source Data Verification

209012 First Trial In Human (FTIH) study requires close, ongoing monitoring of patient data to ensure treatments are safe and tolerated by study participants. When onsite monitoring is not permissible due to site/local restrictions (such as with epidemic and/or pandemic), remote monitoring may be employed that ensures all of the following requirements are met:

- Monitoring plan and execution details [remote source data monitoring (rSDV) method and scope of activities] are outlined in the Study Monitoring Plan
- Remote monitoring method to be employed as permitted by local regulations, agreed upon by study site and approved by IRB/IEC
- Appropriate security systems/provisions are in place to ensure protection of patient data and shared information
- Participants sign ICF including disclosure of remote monitoring for (redacted/anonymized) patient data with security provisions in place

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in the substudies.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing:
  - Refer to Inclusion Criteria in the substudy specific sections for Screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at all times indicated in the SOA.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • Reticulocytes		WBC count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Flow cytometry	CD3/CD4/CD8			
Clinical Chemistry[a]	BUN[b]	Potassium	AST (SGOT)	Total & direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	Chloride
	Albumin	Phosphorus	LDH	Urea
		Magnesium	Bicarbonate	
Coagulation	INR, PT, and aPTT, Fibrinogen			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• CMV IgG and PCR • TSH with free T4 • CRP • Uric acid • GFR or 24 hour Urine • Follicle-stimulating hormone (as needed in women of non-childbearing potential only) • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochete bacterium). • Ferritin • Serum troponin • NT-proBNP / BNP			

a. Details of liver chemistry monitoring criteria and required actions and follow-up assessments after liver monitoring event are given in Section 8.2.1. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

b. Either BUN or UREA tests are acceptable.

c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Note: All study-required laboratory safety assessments will be performed by a local laboratory with the exception of alleles HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1/LAGE-1a expression. The results of the HLA and NY-ESO-1/LAGE-1a tests must be entered into the eCRF.

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = Aspartate aminotransferase; BNB = B-type natriuretic peptide; BUN = blood urea nitrogen; CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein Barr virus; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; NT-proBNP = N-terminal group pro-BNP; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cells.

12.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

12.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Grade ≥3 CRS, ICANS, or GVHD, all cases of aplastic anemia, and all cases of GBS or other demyelinating neuropathies must be reported within 24 hours as SAEs.

12.3.3. 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

12.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign a grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), v5.0, except for the following:

- CRS grading will be based on [Lee, 2019] and include Fever, Hypoxia and Hypotension. Organ toxicities associated with CRS will be graded according to NCI-CTCAE v5.0 and do not influence CRS grading.
- ICANS grading will be based on [Lee, 2019]. Organ toxicities associated with ICANS will be graded according to NCI-CTCAE v5.0 and do not influence ICANS grading.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to GSK. However, **it is very**

important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.

- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

12.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor/SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone or email does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

12.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

12.4.1. 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 enrollment.

12.4.2. Contraception Guidance

Participants should be informed that treatment with fludarabine, cyclophosphamide and/or genetically engineered T cells may have adverse effects on a fetus in utero. Furthermore, while it is not known if such treatment has transient adverse effects on the composition of sperm, the investigator should advise fertile male participants to consider collecting and storing viable sperm prior to undergoing lymphodepletion, given that cyclophosphamide may result in partial (oligospermia) or total (azoospermia) sterility.

Participants who are WOCBP must use a barrier method (male condom) and should comply with one of the methods in the table below. Male participants should use a male condom and should also be advised of the benefit for a female partner to use one of the methods in the table below.

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods 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 [b]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS) [b]
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 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[b] oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation [b] 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. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.*

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. 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: Male condom and female condom should not be used together (due to risk of failure with friction).

Participants 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.

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

Contraception is mandated from the start of study intervention and for the period defined in Table 2, based on the study treatments received

Table 2 Time Periods for Contraception Usage

Study Intervention Received	Contraception to continue from start of study intervention through longest of all intervals defined below based on all treatments received
Fludarabine	6 months after last dose of fludarabine
Cyclophosphamide	Time after last dose of cyclophosphamide: Females – 12 months Males – 6 months
NY-ESO-1 specific T cell infusion	A minimum of 12 months after NY-ESO-1 specific T-cell infusion. In the event that there is still evidence of persistence of gene modified cells in the participant's blood beyond 12 months, contraception to continue until notification by Sponsor that NY-ESO-1 specific T cells are not detected in blood for 2 consecutive times.

The Sponsor will notify the site once the participants' persistence is below the level of detection for 2 consecutive times.

12.4.3. Collection of Pregnancy Information:

Male participants with partners who are or become pregnant

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

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.

- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the Investigator, will be reported to GSK as described in Section 12.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention if possible.

12.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, DNA analysis will be conducted on blood, plasma, and tumor biopsies per local regulations and IRB/IEC.
- DNA samples will be used for research related to NY-ESO-1 specific TCR engineered T cells or cancer indication(s) under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to NY-ESO-1 specific TCR engineered T cells and cancer indications under study. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome, as appropriate.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to NY-ESO-1 specific TCR engineered T cells. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on NY-ESO-1 specific TCR engineered T cells (or study interventions of this class) or indications under study continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.5.1. Companion Diagnostics

US Food and Drug Administration states that an *in vitro* companion diagnostic device (IVD) could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify participants who are most likely to benefit from a particular therapeutic product;
- Identify participants likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product;
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness;
- Identify participants in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.

Global regulatory requirements for IVD companion diagnostic tests are evolving. If a DNA-based IVD companion diagnostic device might be needed to identify participants who are appropriate for the GSK medicinal product(s) under investigation in this protocol, then GSK should collect and retain DNA samples from participants who carry the genetic variant of interest as well as DNA samples from participants who do not carry the genetic variants of interest to validate the performance of the companion diagnostic. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis. Any IVD companion diagnostic research objectives should be described in participant ICFs.

12.6. Appendix 6: Guidelines for Assessment of Disease, Disease Progression, and Response Criteria

12.6.1. RECIST v1.1 Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a Baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/callipers to measure the size of the lesion, is required [Eisenhauer, 2009].

CT and MRI: Contrast enhanced CT with 5 mm contiguous slices is recommended. Minimum size of a measurable Baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: If brain scans are required, then contrast-enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion:

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of the following:

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.
- Additionally, lymph nodes can be considered pathologically enlarged and measurable if ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At Baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease:

The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-measurable only disease:

The presence of only non-measurable lesions.

Note: non-measurable only disease is not allowed per protocol.

Baseline Definition of Target Lesions (TLs) and Non-Target Lesions (NTLs)

Measurable lesions (see definition above) up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected based on their size (measurable diameters) and their suitability for accurate repeated measurements.

All other lesions or sites of disease should be recorded as non-target lesions at screening/baseline and should be followed qualitatively. Non-target lesions will be grouped by organ. Measurements are not required, rather the status of non-target lesions should be determined as "present," "absent," or in rare cases "unequivocal progression" during follow up.

Additional guidance for selection of target and non-target lesions at screening/baseline:

- For selection of target lesions, paired organs such as the lungs or kidneys are each considered together as a single organ, and no more than 2 lesions should be recorded as target lesions within the pair. The skin and all lymph nodes are each considered a single organ for purposes of target lesion selection.
- Lymph nodes of pathological size with short-axis diameters of 10 mm to <15 mm should be recorded as non-target lesions.
- Lesions identified by clinical assessment (superficial skin lesions) only should be followed as non-target lesions when other suitable target lesions are available.
- Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.
- Lesions that have been previously irradiated and have since progressed may be considered as target lesions.
- Lesions which are biopsied at baseline should be considered non-target lesions. If there is only 1 measurable lesion and non-target lesions are absent or not accessible, Medical Monitor (or designee) must be consulted and biopsy may be performed if there is no anticipated risk of interfering with measurement of single lesion.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by CT or MRI can be considered measurable (soft tissue component). Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

Response Criteria

Evaluation of target lesions:

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters (e.g. percent change from Baseline).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Applicable (NA): No target lesions at Baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10 mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at Baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g. 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from Baseline and percent change from nadir.

Evaluation of non-target lesions:

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at Baseline must be non-pathological (e.g., <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at Baseline ≥10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- Not Applicable (NA): No non-target lesions at Baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g., non-target response does not have to be "Not Evaluable").

New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at Baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the Investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of overall response

Table 3 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for participants with measurable disease at Baseline.

Table 3 Evaluation of Overall Response for Participants with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NA=Not applicable, and NE=Not Evaluable

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined

by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the Investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 28 days.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria:

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

12.6.2. iRECIST Guidelines

iRECIST is based on RECIST v1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed according to the rules described below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as meeting all of the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** may be discontinued from study intervention at site-assessed first radiologic evidence of PD. It is strongly preferred to obtain the repeat tumor imaging, when feasible, for confirmation of PD by iRECIST.

In a clinically unstable participant, if the Investigator decides to continue treatment, following consultation with the Sponsor medical monitor, the participant may continue to receive study intervention. The tumor assessment should be repeated at least 4 weeks and up to 12 weeks later to confirm PD by iRECIST. Images should continue to be sent in to the central imaging vendor for potential central review.

If repeat imaging does not confirm PD per iRECIST and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study intervention.

If a participant has confirmed radiographic progression (iCPD) as defined below, study intervention phase should be discontinued; however, if the participant is achieving a clinically meaningful benefit, continuation of study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in the SOA and submitted to the central imaging vendor.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST v1.1 Progression

Until radiographic disease progression based on RECIST v1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST v1.1 Progression

For participants who show evidence of radiological PD by RECIST v1.1, the Investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management [see Table 4]). This decision should be based on the participant's overall clinical condition. (See discussion of clinical stability above).

Tumor flare may manifest as any factor causing radiographic progression per RECIST v1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at Baseline to ≥20% and ≥5 mm from nadir
  - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST v1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at Baseline
- Development of new lesion(s)

iRECIST defines response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST v1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at Baseline by RECIST v1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for Baseline lesion assessment in RECIST v1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at Baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

At the confirmatory imaging visit assessment, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST v1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST v1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST v1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen (see Figure 5). This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, continuation of study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in the SOA and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudo-Progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, doing so for the first-time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions.
- New lesions

- New lesions appear for the first time
- Additional new lesions appear
- Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

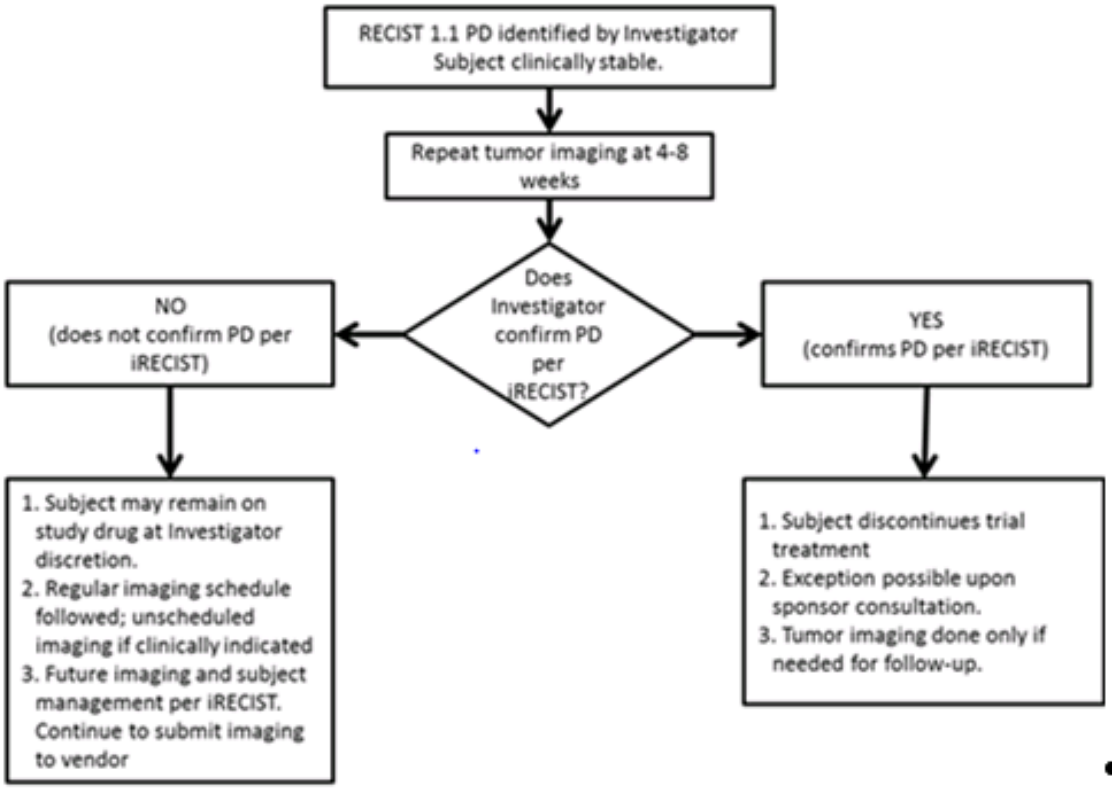
Additional details about iRECIST are provided in the iRECIST publication [Seymour, 2017].

Table 4 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST v1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study intervention at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors v1.1.

Figure 5 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



iRECIST = Modified RECIST 1.1; PD = progressive disease.

12.7. Appendix 7: 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 participants. During lymphodepletion, supportive care should be provided to participants as per local institutional guidelines, based on established oncology practice guidelines for chemotherapy administration and supportive care.

All participants should be hospitalized for at least 3 days after the T-cell infusion. Staff treating trial participants should be experienced in acute post-transplant care and the management of associated toxicities (e.g., cytopenias, cytokine release syndrome (CRS), autologous graft versus host disease).

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

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

See additional supportive guidance in corresponding section within the substudy for substudy specific details, when applicable.

12.7.1. 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 or an alternative per institutional practice. It is recommended all participants 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.

In participants with infusion-related reaction Grade ≤2, infusion may be restarted once resolved to Grade <1. The bag of cells that was being infused prior to reaction, cannot be used beyond 45 min after thawing. Infusion-related reactions Grade 3 or higher during infusion should be reported to Sponsor promptly.

12.7.2. Infection

Additional measures to treat and prevent infection are outlined below. In particular, fever and neutropenia should be aggressively managed as well as pre-emptive influenza

therapy and other standard therapies for immunocompromised hosts, in accordance with institutional guidelines. For participants with indwelling central lines, consider increased surveillance to monitor for catheter-associated infections.

12.7.2.1. *Pneumocystis carinii* Pneumonia (PCP)

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

12.7.2.2. Herpes Simplex, Varicella Zoster and Epstein Barr virus (EBV)

All participants should receive prophylaxis with acyclovir (800 mg twice daily) or valacyclovir (500 mg twice daily) for one year initiated prior to lymphodepletion, or in accordance with institutional guidelines and labels.

12.7.2.3. Cytomegalovirus

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

If a participant experiences prolonged or secondary pancytopenia or lymphopenia, additional monitoring for viral reactivation should be considered and treatment for viral infection initiated if necessary. A strategy for management of pancytopenia or bone marrow failure is described in Section 12.7.7.

12.7.2.4. Hepatitis B Prophylaxis

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

Additional considerations will be left to the Investigator's discretion in accordance with label recommendations and institutional guidelines.

12.7.2.5. Syphilis

Participants will be screened for syphilis before leukapheresis and before lymphodepletion. Participants with positive Screening results should be evaluated by an

infectious diseases consultant. If determined to have syphilis infection, the participant should be treated as needed before the study procedure.

12.7.2.6. Other Anti-Microbial Prophylaxis

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

If patient has prolonged leukopenia, consider vigilance for latent viral infections.

If a participant presents with severe or gross hematuria, consider checking for BK viruria and viremia.

If a participant requires anti-microbial treatment associated with risk of cardiac toxicity, consider close monitoring of cardiac function (Section 9.1.6).

12.7.3. Hematologic and Blood Product Support

Blood product support should be provided to maintain the following:

- Platelets $>10 \times 10^9$/L in the in-patient setting and platelets $>20 \times 10^9$/L in the out-patient setting
- Hb >8.0 g/dL

or as clinically indicated in the judgment of the Investigator, in accordance with institutional practice.

See American Association of Blood Banks Guideline on platelet transfusion [Kaufman, 2015].

12.7.3.1. Irradiated Blood Product

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

12.7.3.2. CMV Screened Blood Products

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

12.7.4. Management of Autoimmunity

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

12.7.5. Management of Cytokine Release Syndrome

CRS is a potentially life-threatening toxicity that has been observed following administration of antibodies and ACTs for cancer. It is defined clinically by symptoms many of which mimic infection, including pyrexia, nausea, diarrhea, headache, fatigue, tachycardia, hypotension, transaminitis, rash, and dyspnea. It is important to evaluate the participant 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]. CRS grading will include Fever, Hypoxia and Hypotension. Organ toxicities associated with CRS will be graded according to NCI-CTCAE v5.0 and do not influence CRS grading [Lee, 2019].

Table 5 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 CCI Assessment and treatment guidelines are provided below in alignment with (the Society for Immunotherapy of Cancer SITC) guidelines [Maus, 2020] and should be followed in conjunction with any local guidelines where available.

If CRS is suspected, a physician with expertise in the management of participants following bone marrow transplant should be consulted.

If CRS is suspected, in addition to assessment for infection, per the Schedule of Assessment (SOA) in individual substudies, the following tests should be conducted

every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed:

- Local tests:
  - Chemistry, hematology, ferritin and coagulation, as well as C-reactive protein (CRP) labs;
- Central tests:
  - Cytokine-profiling as described in Section 9.10.3.

If CRS is suspected, participants deemed to have significant cardiovascular risk factors (per Section 9.1.6) 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.

Table 5 Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment[1,2]	Management Guidelines
1	Temperature ≥38.0 °C	Vigilant supportive care[4] Assess for infection and treat[5]
2	Temperature ≥38.0 °C with hypotension not requiring vasopressors and/or hypoxia requiring the use of oxygen delivered by low-flow nasal cannula (≤6 L/minute) or blow-by.	Monitor cardiac and other organ function Vigilant supportive care[4] Assess for infection and treat[5] Treat hypotension with fluid and pressors Administer O_2 for hypoxia[6] Consider administering tocilizumab ± corticosteroids[7]
3	Temperature ≥38.0 °C with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula (>6 L/minute), facemask, non-rebreather mask, or venturi mask not attributable to any other cause[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 O_2 for hypoxia. Administer tocilizumab ± corticosteroids[7]
4	Temperature ≥38.0 °C with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation) [8]	Manage participant in ICU Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required[6] Administer tocilizumab ± corticosteroids[7]
5	Death[9]	

1. Fever is defined as temperature ≥38°C not attributable to any other cause. 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. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
3. Low-flow nasal cannula is defined as oxygen delivered at 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.
4. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure
5. Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of antimicrobial agents for concurrent bacterial infections, and for treatment of fever and neutropenia as per institutional practice; and antipyretics, analgesics as needed.
6. Given that prolonged fluid resuscitation without pressor use is associated with worse outcome and because early and aggressive supportive care, early use of vasopressors, and timely anti-cytokine therapy are paramount to mitigating life-threatening CRS.
7. Other immunosuppressor agents may be used, including TNFα and IL-1R inhibitors.
8. 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.
9. Grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome.

Source: [Lee, 2019]

Participants requiring immunosuppressive intervention may receive tocilizumab, steroids, or both [Davila, 2014; Lee, 2014; Lee, 2019]. Tocilizumab is a humanized anti-IL-6 receptor antibody that has been approved for the management of severe or life-threatening CRS induced by chimeric antigen receptor (CAR) T cell therapy [Tocilizumab USPI, 2020; Tocilizumab SmPC, 2020].

Per the package insert, the recommended dose of tocilizumab for patients with severe or life-threatening CRS who weigh 30 kg or above is 8 mg/kg, administered intravenously over 1 hour with a total dose not exceeding 800 mg per infusion. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 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].

Per SITC 2020 guidelines:

If CRS does not improve after one dose of tocilizumab, then steroids should be administered with a second dose tocilizumab (e.g. methylprednisolone 2 mg/kg/day or dexamethasone 0.5 mg/kg up to 10 mg/dose). If CRS does not improve after 2 doses of tocilizumab (and steroids), third-line agents, including anakinra, siltuximab, and high-dose methylprednisolone, should be considered. If steroids are used in the management of CRS, a rapid taper should be used once symptoms begin to improve [Maus, 2020].

Use of myeloid growth factors, particularly Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) is not recommended because GM-CSF may theoretically aggravate CRS [Raje, 2019]. Consider holding G-CSF during CRS [Maus, 2020].

Assessment and management of neurological signs and symptoms associated with CRS should include consideration of concurrent occurrence of Immune-effector cell-associated neurotoxicity syndrome (ICANS). See Section 12.7.8 for further details.

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

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

drawn from published case reports and guidelines for the diagnosis and management of acute GvHD following allogeneic transplant [Dignan, 2012].

12.7.6.1. Diagnosis of GvHD

The diagnosis of GvHD is predominantly based on clinical findings and is often one of exclusion (Table 6). Many of these symptoms can also occur in the setting of the preparative regimen, high dose cyclophosphamide, as well as with CRS. Any of these conditions including GvHD can be associated with fever. The skin is the most commonly involved organ, followed by the GI tract and liver. A constellation of symptoms involving these organ systems may be helpful in establishing the diagnosis of GvHD. Diarrhea, rash, fever, and pancytopenia are common toxicities in the GSK3377794 (lete-cel) program where we have the most clinical experience. Mild (Grade 1 or 2) transient transaminitis without cholestasis has been observed.

Table 6 Overview of Clinical Findings/Symptoms of GvHD

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

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

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

Bone marrow suppression is also a feature of transfusion-related GvHD. To minimize the possibility of transfusion-related GvHD, refer to Section 12.7.3.1 for guidance on irradiated blood products.

12.7.6.2. Grading of GvHD

Grading of acute GvHD is based on the stage of dermal, gastrointestinal, and hepatic involvement as described in Table 7. Careful measurement of stool volume and assessment of percentage of body area covered by rash are important for proper grading and treatment.

Table 7 Staging of Dermal, Gastrointestinal and Hepatic Involvement with Acute GvHD

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

With the addition of assessment of functional impairment, grading can be determined using Table 8 [Glucksberg, 1974].

Table 8 Grading of Acute GvHD

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

1. Staging is described in Table 7.
2. Mild, moderate, or severe decrease in performance status

12.7.6.3. 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 start of appropriate therapy.

If GvHD is suspected:

- A physician with expertise in the management of participants following bone marrow transplant should be consulted
- Biopsy of the affected organ(s) should be considered

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

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

General guidelines for first-line treatment based on grade are provided in Table 9 and should be considered in conjunction with input from the consulting physician with bone marrow transplant expertise.

Table 9 Management Guidelines for GvHD

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

1. The use of 'nonabsorbable' steroids (budesonide and beclomethasone) can be considered for acute intestinal GvHD in order to reduce the dose of systemic steroids

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

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

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

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

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

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

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

- ANC ≥1,000/μL for 2 consecutive measurements approximately 7 days apart, and
- Platelet count ≥20,000/μL without transfusion support for 1 week.

Aplastic anemia is a rare hematological disorder characterized by pancytopenia and a hypocellular marrow. Participants are usually symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. The diagnosis of severe aplastic anemia is made in the setting of a hypocellular bone marrow when 2 of the following 3 blood counts are met: ANC <500/μL, absolute reticulocyte count <60,000/μL, and platelet count <20,000/μL, and myelodysplastic syndrome is ruled out. The clinical consequences of aplastic anemia are life-threatening bleeding from thrombocytopenia, and infection as a result of neutropenia. Bacterial and fungal infections are common and a significant cause of morbidity and mortality.

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

- Consult a physician with expertise in the management of aplastic anemia
- Increase the frequency of complete blood counts (CBCs) as clinically indicated.
- Exclude other alternative etiologies such as other drugs, viral causes, etc.
- An early bone marrow biopsy is recommended for clinical diagnosis, with a sample to be provided to the Sponsor for study. Details on tissue collections, kit use, and shipment information can be found in the SRM.
- A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the Sponsor.
- 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 12.7.6 regarding bone marrow suppression as a feature of GvHD.

12.7.8. 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), and the CRS 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. 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.

12.7.8.1. Grading of ICANS

Lee et al. [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) (Table 10). Points are assigned for each of the tasks in Table 10, which are performed correctly. Normal cognitive function is defined by an overall score of 10. The ICE should be used to monitor all participants for ICANS.

Table 10 ICE-Encephalopathy Assessment Tool for Grading of ICANS

Task	ICE Points
Orientation to: year, month, city, hospital	Total of 4 points (one point for each)
Name three objects, for example point to: clock, pen, button	Total of 3 points (one point for each)
Follow simple commands (for example, “Show me 2 fingers” or “Close your eyes and stick out your tongue”	1 point
Write a standard sentence, e.g., ‘our national bird is the bald eagle’	1 point
Count backwards from 100 in tens	1 point

Abbreviation:ICE = Immune Effector Cell-Associated Encephalopathy; ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome.

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

The ICE score is used in grading of ICANS in adults as presented in Table 11.

Table 11 Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score [1]	7 to 9	3 to 6	0 to 2	0 (Participant is unarousable and unable to perform ICE)
Depressed level of consiousness [2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging [4]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema [3]; or Cushing's triad
Motor findings [5]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to Baseline in between

1. See Table 10 for ICE. A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
2. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication)
3. Papilloedema grading is performed according to the modified Frisén scale.
4. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.
5. Tremors and myoclonus associated with immune effector cell therapies do not influence ICANS grading

This table is based on Lee, 2019.

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

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

Brain MRI (or CT Scan if MRI not feasible) must be obtained for all participants as part of leukapheresis eligibility screening. This should be repeated at Baseline prior to lymphodepletion in:

- All participants with a history of CNS metastasis, and
- In participants with no history of CNS metastasisif more than 3 months have elapsed between last brain MRI and the start of lymphodepletion or if they show neurological symptoms consistent with CNS metastasis.

Brain MRI may be performed at other time points, if clinically indicated.

ICE should be measured on the day of T-cell infusion prior to receiving treatment and then at least through Day 8 according to the SOA in individual substudies. If a participant is found to have ICANS, the ICE should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

12.7.8.3. Management of ICANS

The recommended management of ICANS should be based on toxicity grade. Table 12 provides guidance on the management of ICANS and should be implemented in accordance with institutional guidelines.

A neurology consultation should be obtained for all participants with ICANS for thorough neurological evaluation, and recommendations for further testing such as electroencephalogram (EEG) and neuroimaging as indicated.

The following tests should be conducted **every day for the first week** and approximately **every other day thereafter** until symptoms are improving or an alternative diagnosis is confirmed:

- Local tests:
  - Chemistry, hematology, ferritin, and coagulation, as well as C-reative protein (CRP) labs

Per SITC 2020 guidelines:

Across several trials, tocilizumab has failed to resolve symptoms of ICANS, despite alleviating severe CRS [Maus, 2020]. It remains to be determined whether targeting IL-6R in isolation during established CRS is insufficient to prevent subsequent neurotoxicity or if the lack of efficacy is due to tocilizumab's inability to cross the blood-brain barrier. It has been postulated that tocilizumab may worsen ICANS and therefore an assessment of treatment priority may be required between the severity of CRS and ICANS. Alternative IL-6 blockade such as siltuximab or the IL-1 antagonist, anakinra, have been proposed as potential alternatives, but data are lacking on their safety and efficacy.

Corticosteroids have been successfully used for the management of ICANS and seizure prophylaxis has been implemented in some studies, but the ideal dose and duration have not yet been determined [Maus, 2020].

Table 12 Management of ICANS

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 and appropriate such as diagnostic lumbar puncture with measurement of opening pressure if increased intracranial pressure is suspected, or MRI of the spine if the participant has focal peripheral neurological deficits • Consider levetiracetam therapy and EEG if seizure activity is suspected • Consider anti-IL-6 therapy. Tocilizumab[1] may worsen neurotoxicity. Management of neurotoxicity may take precedence over the management of low-grade CRS, but this does not apply to high-grade CRS. Alternative IL-6 blockade may be considered (e.g. siltuximab) or the IL-1 antagonist, anakinra.
2	• As described for **Grade 1 PLUS** • Consider ICU transfer • Consider corticosteroids[2]
3	• As described for **Grade 1 & 2 PLUS** • Corticosteroids are recommended • 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 to 3 days if participant has persistent Grade ≥3 ICANS
4	• As described for **Grade 1 & 2 & 3 PLUS** • Consider neurosurgical consultation for participants with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection

1. Tocilizumab: 8mg/kg iv for patients weighing 30kg or above, administered over 1 hr, max dose 800 mg, doses at least 8 hrs apart.
2. Consider dexamethasone 10 mg IV every 6 hrs (Grade ≤3 ICANS), or methylprednisolone 1 mg/kg IV every 24 hrs for 3 days (Grade 4 ICANS), if refractory to anti-IL-6 therapy, or for ICANS without concurrent CRS; once initiated continue corticosteroids for at least two doses until improvement to Grade 1 ICANS and then taper.

Source: [Maus, 2020].
CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography;
EEG = electroencephalogram; hrs = hours; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome;
ICU = intensive care unit; IL-6 = interleukin-6; IV = intravenous; MRI = magnetic resonance imaging.

Grade 1 ICANS. Grade 1 ICANS is defined as a score of 7 to 9 on the ICE assessment in Table 11. A patient with grade 1 ICANS may have a delay in responses or disorientation to time or place, mild inattention with difficulty in counting numbers backwards, or impairment of handwriting. There may be drowsiness but patients awaken spontaneously, and when prompted, the patient should be able to complete most of the ICE assessment. Grade 1 ICANS may be seen during CRS waxing and waning with febrile episodes.

Grade 2 ICANS. Grade 2 ICANS is defined as a score of 3 to 6 on the ICE assessment as presented in Table 11. Expressive aphasia is the most specific first sign of severe

neurotoxicity and early signs during grade 2 include paraphasic errors (the production of unintended syllables and words during attempts to speak) and verbal perseveration with patients repeating the same words over and over. Patients with grade 2 ICANS are able to communicate their needs but it is effortful. Patients may have depressed level of consciousness but are arousable to voice and the responses may be slowed.

Grade 3 ICANS. Grade 3 ICANS is defined as a score of 0 to 2 on the ICE assessment as presented in Table 11. Patients with grade 3 ICANS have severe global aphasia and are not speaking or following commands even when wide awake and therefore may be unable to complete any of the ICE questions. Alternatively, they may have excessive drowsiness and need tactile stimulus to attend to examiner. Any clinical seizure whether simple partial, complex partial or generalized, and any electrographic seizures would also meet criteria for grade 3 ICANS. If neuroimaging shows new focal or local edema this would also be categorized as grade 3 ICANS. However, intracranial hemorrhage due to coagulopathy or other causes with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.

Grade 4 ICANS. Grade 4 ICANS is defined as patients who have a score of 0 on the ICE assessment due to being unarousable and unable to perform the ICE assessment as presented in Table 11. Stupor and coma may be seen; the stuporous patient only responds by grimacing or drawing away from vigorous or repetitive tactile stimuli and the comatose patient is unarousable and/or unresponsive. This depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication), which is often a complicating factor in sick patients with CRS. Some patients may require intubation for airway protection. In addition, any patient having prolonged or repetitive clinical or subclinical electrographic seizures without return to Baseline in between, or deep focal motor weakness such as hemiparesis or paraparesis would be considered to have Grade 4 ICANS. Patients with symptoms and signs of elevated ICP such as projectile vomiting with headache, depressed consciousness, cranial nerve VI palsies, papilledema, Cushing's triad of bradycardia, hypertension and respiratory depression, decerebrate or decorticate posturing, or diffuse cerebral edema on head imaging would also be considered to have grade 4 ICANS.

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

12.7.9. Chemotherapy Symptom Management

Cyclophosphamide and fludarabine are used as conditioning chemotherapy in this study to cause lymphodepletion and facilitate expansion of the infused T cells. Symptoms associated with the use of cyclophosphamide and fludarabine are included in the product labels. Refer to the most current product labels, and substudy specific sections for details of prohibited medications.

12.7.9.1. Management of Neutropenia

The conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF is recommended in all participants. G-CSF (e.g., filgrastim) should be used for management of neutropenia

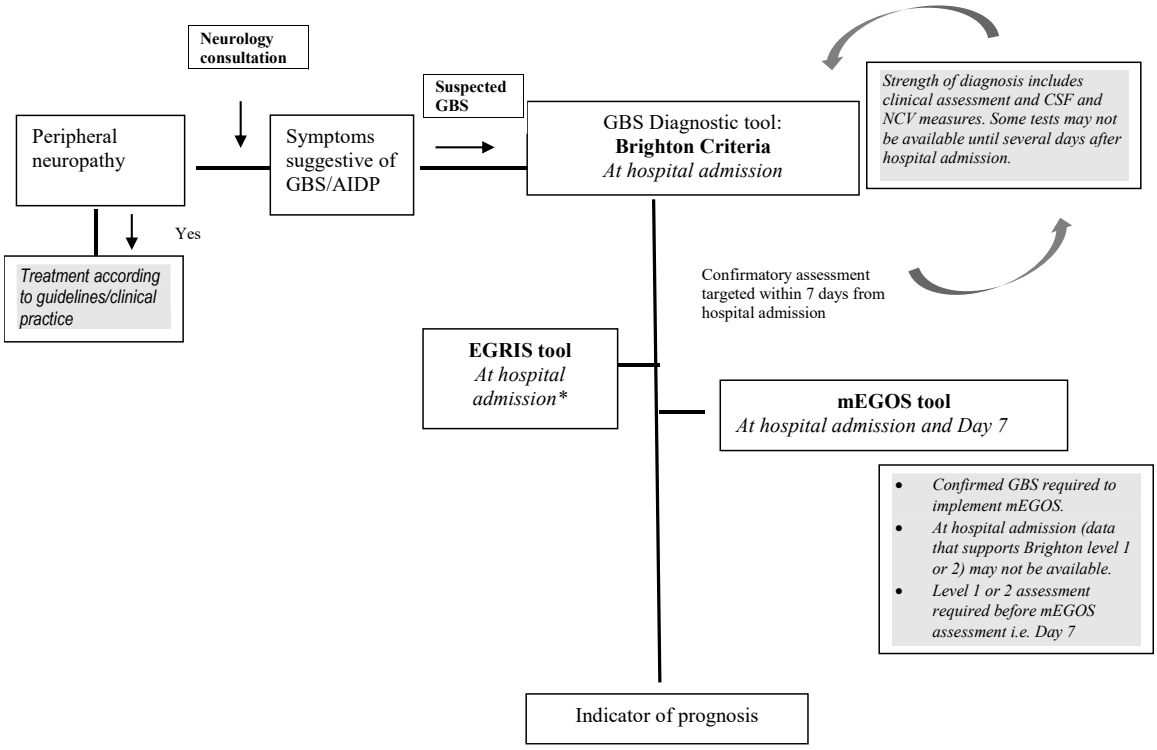
according to ASCO guidelines [Smith, 2015]. G-CSF should be given starting ~24 hours after the administration of chemotherapy until resolution of neutropenia (reaching an ANC of at least 2×10^9/L to 3×10^9/L or as per institutional practice).

Long-acting (pegylated) G-CSF may be given in preference to short acting daily G-CSF in accordance with institutional standard practice. Pegylated G-CSF will be given as one dose ~24 hours post the final dose of cyclophosphamide.

12.7.10. Management of Guillan-Barré Syndrome (GBS)

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

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



*Please refer to algorithm for treatment described in Figure 6.

Additional details specific to the neurology consultation are included in Appendix 8 (Section 12.8).

12.7.10.1. Neurological Symptoms

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

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

- Areflexia (or decreased tendon reflexes) in weak limbs

Additional symptoms:

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

12.7.10.2. Brighton Key Diagnostic Criteria

At admission and confirmation within 7 days of admission:

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

12.7.10.3. Erasmus 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

12.7.10.4. Modified Erasmus GBS Outcomes Score (mEGOS)

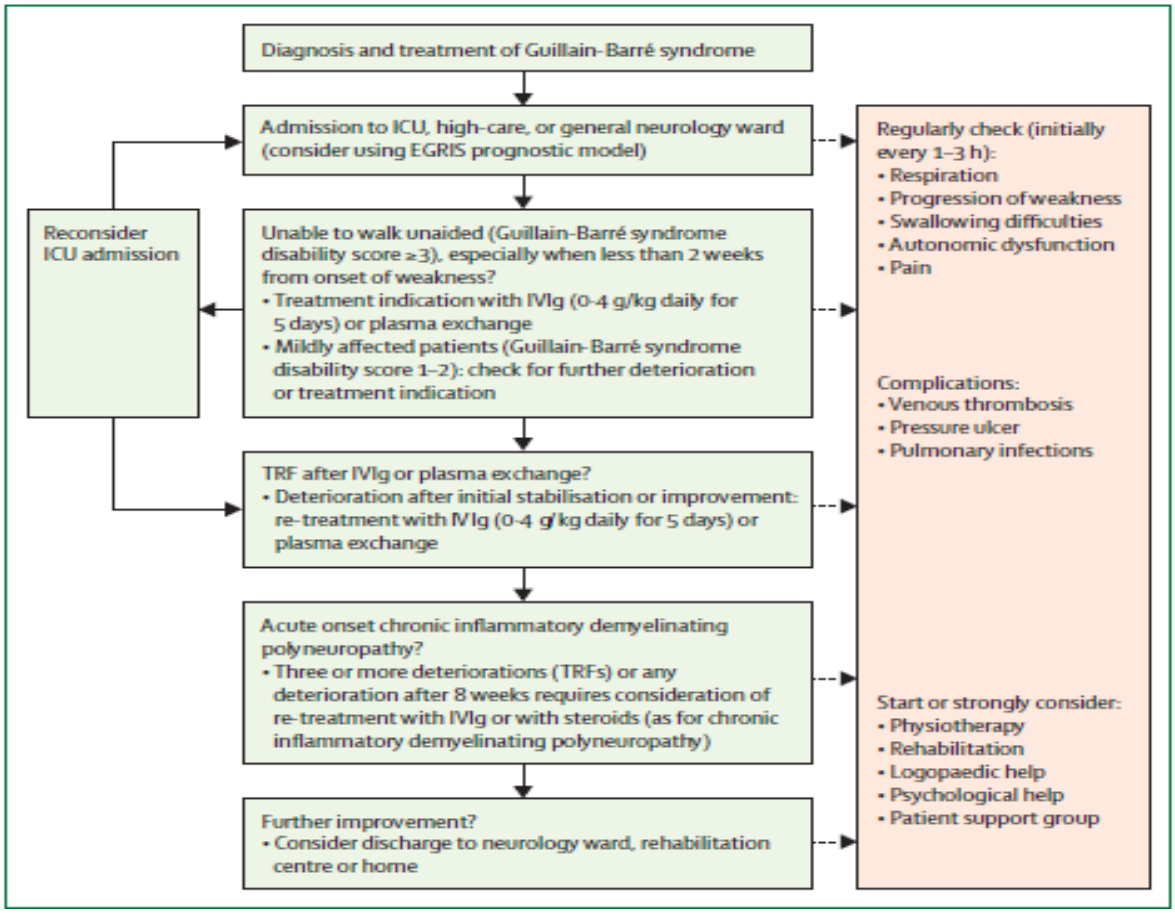
Parameters required at hospital admission and 7 days later [Walgaard, 2011]:

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

12.7.10.5. Summary of Diagnosis and Treatment for GBS

Additional information on the diagnosis and management of GBS (Figure 6) can be found in a review article on GBS [Willison, 2016].

Figure 6 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.

12.8. Appendix 8: Neurology Consultation – Further Guidelines for Signs and Symptoms Suggestive of Guillain-Barré Syndrome

For patients presenting with neurological events, a confirmed diagnosis of peripheral neuropathy should be treated according to local guidelines and/or clinical practice.

However, any patient with presenting signs and symptoms suggestive of GBS (see protocol, Section 12.7.10.1), must be further evaluated by a neurologist according to diagnostic guidance for GBS using the **Brighton diagnostic criteria** (Fokke, 2014] see Table 13 below). The initial assessment at hospital admission should be further verified within 7 days of initial assessment, following availability of all test results as listed:

Table 13 Brighton Diagnostic Criteria

Diagnostic Criteria	Level of Diagnostic Certainty			
	1	2	3	4
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	+	+[1]	-	±
CSF protein concentration > normal value	+	±[1]	-	±
Nerve conduction study findings consistent with one of the subtypes of GBS	+	±	-	±
Absence of alternative diagnosis for weakness	+	+	+	+

1. If CSF not collected or results not available, nerve conduction studies must be consistent with diagnosis of GBS (modified from Fokke, 2014).

+ = present; - = absent; ± = present or absent; GBS = Guillain-Barré Syndrome.

12.8.1. Additional Assessments for Suspected GBS at Hospital Admission

12.8.1.1. Risk of Respiratory Insufficiency Assessment

An assessment of the probability of risk of respiratory insufficiency during the first week following admission of suspected GBS is required using the **Erasmus GBS Respiratory Insufficiency Score (EGRIS**) tool (total score 0 to 7) [Walgaard, 2010].

Please access link to assessment tool and record total score in eCRF.
https://qxmd.com/calculate/calculator_527/erasmus-gbs-respiratory-insufficiency-score-egris

Assessment at hospital admission to include:

- Days of onset of weakness and admission
- Facial and/or bulbar weakness at admission

- Medical Research Council score

The **Medical Research Council** score includes assessment for 6 muscle groups, including shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors on both sides. The MRC score of an individual muscle group range from 0 to 5:

Assessment	Score
No visible contraction	0
Visible contraction without movement of the limb	1
Active movement of the limb, but not against gravity	2
Active movement against gravity over (almost) the full range	3
Active movement against gravity and resistance	4
Normal	5

Source: [Van Koningsveld , 2007].

The MRC total scores range from 60 (normal) to 0 (quadriplegic). The total score should be included in the eCRF assessment for EGRIS.

12.8.1.2. Prognostic Tool for Assessment of GBS Outcome at Hospital Admission

An assessment of prognosis using the **modified Erasmus GBS Outcomes Score (mEGOS**) (total score 0 to 9) for diagnosed cases of GBS [Walgaard, 2011] should also be performed. Early assessment following hospital admission includes assessment of the following:

- Age (years) at onset: ≤ 40, 41 – 60, > 60
- Preceding diarrhoea (in 4 weeks preceding onset of weakness): absent/present
- MRC sum score (see above): 0 – 30, 31 - 40, 41 – 50, 51 – 60

Please access link to assessment tool and record total score in eCRF.

https://qxmd.com/calculate/calculator_529/modified-erasmus-gbs-outcome-score-egos-at-day-7-of-admission

12.8.2. Assessments Post Hospital Admission for GBS

12.8.2.1. Brighton Criteria

The initial assessment at hospital admission should be further verified within 7 days of initial assessment, following availability of all test results.

12.8.2.2. Prognostic Tool for Assessment of GBS Outcome at Day 7 Post Hospital Admission

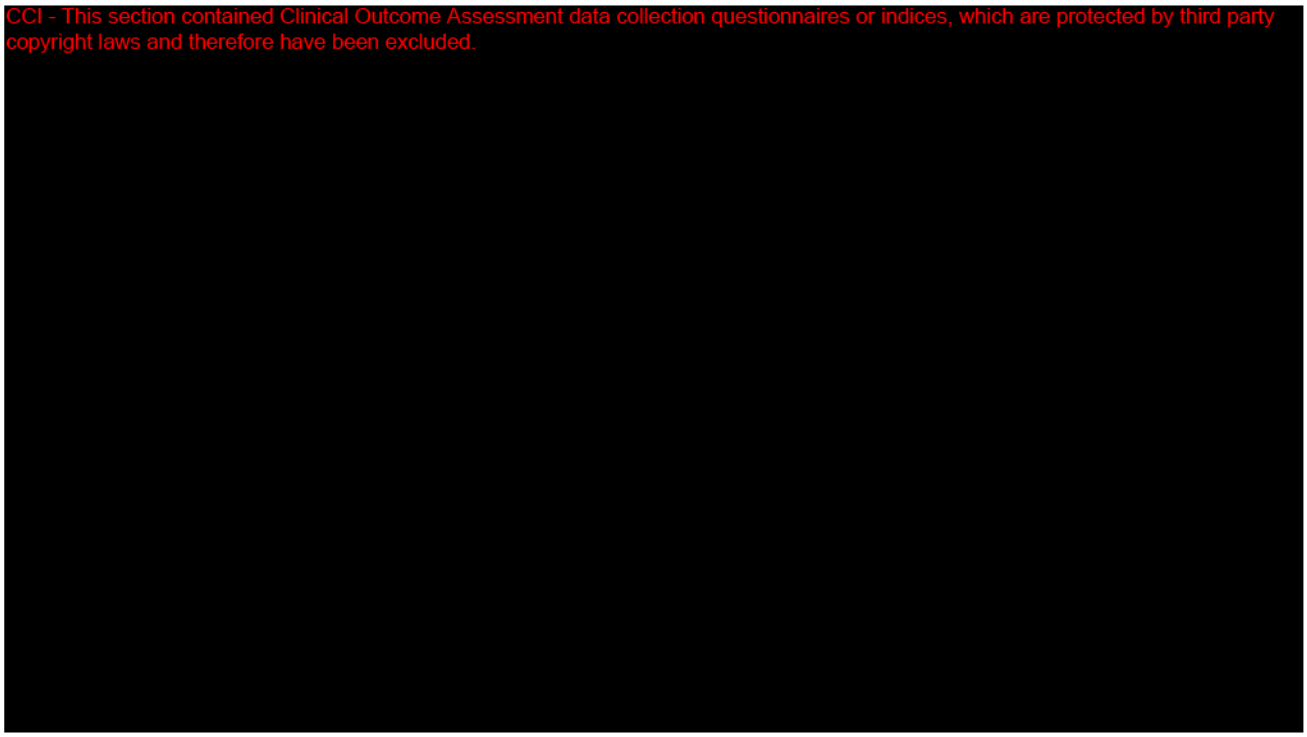
An assessment of prognosis using the **modified Erasmus GBS Outcomes Score (mEGOS**) (total score 0 to 9) for diagnosed case of GBS [Walgaard, 2011]. Assessment following Day 7 hospital admission includes assessment of the following:

- Age (years) at onset: ≤ 40, 41 – 60, > 60
- Preceding diarrhoea (in 4 weeks preceding onset of weakness): absent/present
- MRC sum score (see above): 0 – 30, 31 - 40, 41 – 50, 51 – 60

Please access link to assessment tool and record total score in eCRF.

https://qxmd.com/calculate/calculator_529/modified-erasmus-gbs-outcome-score-egos-at-day-7-of-admission

- **Brighton criteria -** the initial assessment at hospital admission should be further verified *within* 7 days of initial assessment, following availability of all test results.


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.

12.10. Appendix 10: mTPI-2 Design Simulation Results

Simulations on the mTPI-2 design were conducted assuming either a 10% or 20% toxicity rate for the low dose ($0.1 \times 10^9 – 0.8 \times 10^9$ transduced T cells) and a 10%, 20%, 30%, or 40% toxicity rate for the high dose ($1 \times 10^9 – 8 \times 10^9$ transduced T cells). The maximum tolerated dose is defined as the dose with DLT rate of 30%. The simulation results are shown in the tables below which demonstrates that mTPI-2 is a robust study design under all scenarios.

Table 14 shows the results of the simulation. Based on the preclinical evidence and observed GSK3337794 toxicity data, we assume the moderate (20%) or borderline (30%) high dose toxicities are the most likely scenarios for GSK3901961 & GSK3845097. For these scenarios, highlighted in bold, we see that average observed toxicity rate is very close to the true underlying rate for the high dose and lower than the true underlying rate for the low dose. The average number of participants who experienced DLTs at the high dose is less than 2 out of an average of 8 participants when there is a borderline toxicity rate and less than 2 out of an average of 7 participants if there is a moderate toxicity rate. These results support our claim that the chosen design will be protective against over dosing. Additionally, the maximum tolerated dose is chosen >91% of the time when there is a moderate toxicity rate in the high dose and >76% of the time when there is a borderline toxicity rate in the high dose, which shows that the design is robust in correctly choosing the correct MTD under different underlying dose-DLT rate models.

Table 14 Design Simulation Results

True DLT rates	Low: 0.1 High: 0.1	**Low: 0.1 High: 0.2**	**Low: 0.1 High: 0.3**	Low: 0.1 High: 0.4	**Low: 0.2 High: 0.2**	**Low: 0.2 High: 0.3**	Low: 0.2 High: 0.4
Average Observed Toxicity Rate							
Low Dose	0.07	**0.09**	**0.09**	0.09	**0.17**	**0.18**	0.18
High Dose	0.10	**0.20**	**0.30**	0.42	**0.20**	**0.31**	0.43
Average Number of DLTs							
Low Dose	0.02	**0.08**	**0.17**	0.30	**0.17**	**0.37**	0.62
High Dose	0.60	**1.23**	**1.90**	2.55	**1.21**	**1.82**	2.42
Average Sample Size							
Low Dose	0.15	**0.76**	**1.74**	2.94	**0.86**	**1.88**	3.14
High Dose	6.02	**6.13**	**6.30**	6.36	**6.04**	**6.07**	6.03
Total Dosed	6.17	**6.89**	**8.04**	9.29	**6.90**	**7.95**	9.17
Percent picked as Maximum Tolerated Dose (MTD)							
No Dose	0.00	**0.00**	**0.00**	0.00	**0.01**	**0.02**	0.02
Low Dose	0.01	**0.07**	**0.21**	0.42	**0.09**	**0.22**	0.42
High Dose	0.99	**0.93**	**0.79**	0.58	**0.91**	**0.76**	0.55

12.11. Appendix 11: Abbreviations and Trademarks

1L	First line
2L	Second line
ABW	Adjusted body weight
ACT	Adoptive T-cell therapy
AE	Adverse event
AESI	Adverse events of special interest
AIDP	Acute inflammatory demyelinating polyneuropathy
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Antithymocyte globulin
AUC(0-t)	Area under the concentration-time curve over the dosing interval
BUN	Blood urea nitrogen
CA	Competent Authority
CAR	Chimeric antigen receptor
CBC	Complete blood count
CD3/CD4/CD8	Cluster of differentiation 3/ cluster of differentiation 4/ cluster of differentiation 8
CDC	Center for Disease Control
CFR	Code of federal regulations
cfDNA	Cell-free DNA
CI	Confidence Interval
CIOMS	Council for international organizations of medical sciences
CKD-EPI	Chronic kidney disease epidemiology collaboration
cm	Centimetres
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration;
CMV	Cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated standards of reporting trials
CPD	Confirmed progression
CPK	Creatine phosphokinase
CR	Complete response
CRES	CAR T-cell related encephalopathy syndrome
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome

CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
D	Day
dL	Decilitre
CCI	[redacted]
DLCO	Diffusing capacity of the lung for carbon monoxide
DNA	Deoxyribonucleic acid
DOR	Duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram(s)
ECHO	Echocardiography
eCOA	electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EMG	Electromyography
EOT	End of treatment
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FEV1	Forced expiratory volume in 1 second
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GBS	Guillain-Barré Syndrome
GCLP	Good clinical laboratory practice
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	Glaxosmithkline
GvHD	Graft versus host disease
Hb	Haemoglobin
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HbcAb	Hepatitis B core antibody
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus

HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
hr	Hour
HRT	Hormone replacement therapy
HTLV	Human T-lymphotropic virus
IB	Investigator's brochure
IBW	Ideal Body Weight
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
ICF	Informed consent form
ICH	International council on harmonization of technical requirements for registration of pharmaceuticals for human use
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
IEC	Independent ethics committees
IFN	Interferon
IFNγ	Interferon, gamma
IgG	Immunoglobulin G
IL	Interleukin
IL-1R	Interleukin-1 Receptor
INR	International normalized ratio
CC[redacted]	[redacted]
iPR	iRECIST progressive disease
irAEs	Immune-related AEs
IRB	Institutional review board
iRECIST	Modified RECIST 1.1 for immune-based therapeutics
iSD	iRECIST stable disease
ITT	Intent to treat
IUD	Intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVD	In vitro companion diagnostic device
kg	Kilograms
LAM	Lactational amenorrhoea method
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
m^2	Meters squared
mAb	Monoclonal antibody
MCH	Mean corpuscular haemoglobin
MCV	Mixed cell volume

MCE	Multi-component engineering
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mITT	Modified Intent to treat
mL	Millilitre
µL	Microliter
mm	Millimetres
MRCLS	Myxoid/round cell liposarcoma
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
mTPI-2	Modified Toxicity Probability Interval 2
MUGA	Multigated acquisition scan
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NIH	National Institutes for Health
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NSCLC-SAC	Non-small-cell lung cancer Symptom Assessment Questionnaire
NY-ESO-1	New York esophageal antigen-1
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCI	Potential clinical importance
PCP	Pneumocystis carinii Pneumonia
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed death receptor-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PFT	Pulmonary function test
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PT	Prothrombin time
QTc	Corrected QT interval duration
QTcB	QT duration corrected for heart rate by Bazzetts's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RBC	Red blood cell

CCI [redacted]	
RECIST	Response Evaluation Criteria in Solid Tumors
RT-qPCR	Reverse transcriptase polymerase chain reaction
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCT	Stem cell transplant
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOA	Schedule of assessments
SoC	Standard of care
SRM	Study reference manual
SRT	Safety Review Team
SS	Synovial sarcoma
SUSAR	Suspected unexpected serious adverse reactions
T4	Thyroxine 4
TCR	T-cell receptor
TGF	Transforming growth factor
TLC	Total lung capacity
TLTs	Treatment Limiting Toxicities
Tmax	Time to maximum concentration
TMB	Tumor mutational burden
TMDD	Target-mediated drug disposition
TME	Tumor microenvironment
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
CCI [redacted]	[redacted]
ULN	Upper limit of normal
UPD	Unconfirmed progression
CCI [redacted]	[redacted]
W	Week
WBC	White blood cell
WHO	World health organization
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ADVAIR

Trademarks not owned by the GlaxoSmithKline group of companies
Chiron RIBA
MedDRA
SAS
WinNonlin

12.12. Appendix 12: List of Substudies

Substudy Number	Substudy Title	GSK number	Anticipated number of participants	Indications	Countries where substudy will be active
1	GSK3901961 [NY-ESO-1(c259)TCR engineered T cells co-expressing the α-chain of the CD8 co-receptor] in previously treated (2L+) HLA-A*02^{+} participants with NY-ESO-1 and/or LAGE-1a advanced SS, MRCLS, or NSCLC	GSK3901961	29	SS, NSCLC, MRCLS	Australia, Canada, Germany, Netherlands, Sweden, USA,
2	GSK3845097 [NYESO-1(c259) TCR engineered T cells co-expressing the dnTGF-βRII receptor] in previously treated (2L+) HLA-A*02^{+} participants with NYESO-1^{+} and/or LAGE1a+ advanced SS or MRCLS	GSK3845097	19	SS, MRCLS	Australia, Canada, Germany, Netherlands, Sweden, USA,
3	GSK4427296 [NYESO-1(c259) TCR engineered T cells using the Epi-R manufacturing process] in previously treated (2L+) HLA-A*02^{+} participants with NYESO-1^{+} and/or LAGE1a+ advanced SS or MRCLS	GSK4427296	19	SS, MRCLS	USA only
Overall projected sample size			67	SS, NSCLC, MRCLS	

12.13. Appendix 13: Master Protocol Document History

DOCUMENT HISTORY Original protocol and all amendments listed in reverse chronological order.				
Master Protocol Format	**Amended Documents***	**Amendment Number**	**Date**	**Document Number**
Master Protocol split into separate documents	**Core Protocol**	Amendment 4	27 May 2022	TMF-14682560
	Substudy 1			TMF-14682591
	Substudy 2			TMF-14682598
	Substudy 3			TMF-14682622
	Core Protocol	Amendment 3	20-December-2021	TMF-14357914
	Substudy 1			TMF-14357929
	Substudy 2			TMF-14357930
	Substudy 3 (new)			TMF-14357932
Master Protocol as single document	Master Protocol with 3 sections: Core, Substudy 1 and Substudy 2	Amendment 2	04-November-2021	TMF-14137790
		Amendment 1	21-May-2021	TMF-13779299
		Original Protocol	02-December-2019	2019N419717_00

* The most current version of each document is in **bold and underlined**.

13. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC). Below is history of prior protocol amendments.

13.1. Amendment 1 (21 May 2021)

Overall Rationale for Amendment 1:

The primary rationale for protocol Amendment 1 is .

1. Changes to Substudy 1 and 2 Inclusion criteria relative to disease status requirements to allow participants with advanced disease diagnosis to undergo target expression screening; participants with evidence of radiological or clinical disease progression will be able to undergo leukapheresis; initiation of lymphodepletion will require evidence of disease progression from prior line of therapy by RECIST v1.1.
2. Changes to Substudy 1 Inclusion and Exclusion criteria language relative to prior lines of treatments for NSCLC participants to allow those who have received any PD-1/PD-L1 checkpoint blockade therapy and, in the same or different line of treatment, any platinum containing chemotherapy. NSCLC participants with actionable genetic aberrations may also be included if they have exhausted the targeted standard of care therapy.
3. Clarifications to Substudy 1 and 2 lymphodepleting chemotherapy dose adjustments to ensure adequate consideration given to prior anti-cancer therapies (systemic and radiation exposure), renal function (for fludarabine) as well as use of adjusted body weight (for cyclophosphamide when necessary).
4. Protocol language optimization to harmonize with program.
5. Allowing potential future inclusion of a limited number of patients who progressed following clinical benefit (PR, CR, SD >/= 3 months) from infusion with letetresgene autoleucel (GSK3377794, lete-cel) on a GSK sponsored trial.

Section # and Name	Description of Change	Brief Rationale
Core protocol		
1. Synopsis 4. Objectives and Endpoints	Reformatted Secondary Objectives and Endpoints into "Secondary – Efficacy", "Secondary – Safety" and "Secondary – Pharmacokinetics".	To clarify subcategories of secondary objectives.
	CCI [redacted]	
	Combined Frequency and severity of Adverse Events (AEs), Serious AEs (SAEs) and AEs of Special Interest (AESIs) as one single endpoint.	Standardization of reporting.
	Optimized description of Secondary – Pharmacokinetics objectives and endpoints.	Clarification of Pharmacokinetics plan.
	Updated list of abbreviations.	Finalization of table.
1. Synopsis 5. Design	Minor update to study schema: - To standardize designated populations as participants with relapsed/refractory advanced tumors. - To standardize designated SS population in Substudies 1 and 2 as participants with "metastatic or unresectable" SS. - To standardize designated NSCLC population in Substudy 1 as participants with "metastatic" NSCLC.	Harmonization of population designations throughout protocol.
1. Synopsis 5. Design	Inclusion of detailed description of Participant Journey, in alignment with Figure 1 Participant Journey Schema.	Clarification of Participant Journey steps.
	Inclusion of provision for allowing target expression screening tests, leukapheresis and manufacture to be conducted under separate GSK-sponsored protocol or substudy of this protocol.	To facilitate pre-screening (eventually performed in other protocols), and to allow for re-allocation of participants onto other suited protocols/substudies when available.
1. Synopsis 5. Design	Optimization of Treatment Fitness and Eligibility criteria prior to Lymphodepletion	Removed requirement for repetition of all eligibility criteria assessments that were already met prior to leukapheresis. Replaced by a Treatment Fitness assessment of the safety criteria in consultation with Medical Monitor.
3.2 Background 3.2.2 GSK3377794 (letetresgene autoleucel, let-cell)	Removed table of GSK3377794 Clinical studies.	To refocus background section and improve readability of document.

Section # and Name	Description of Change	Brief Rationale
5.1. Overall Design	Included reference to definition of sentinel participant as those to receive split dosing per Core Section 8.1.2.	To better introduce what a sentinel participant is.
5.3. Number of Participants	Clarification of projected number of participants (48) expected for dose confirmation and expansion in Substudies 1 and 2 combined.	Clarified sample size projection.
6.2. Screening under other GSK studies (new section added)	Participants screened or enrolled in other GSK studies may be considered for enrollment to this study, where it is IRB/IEC approved, on a case-by-case scenario.	To allow for target expression eligibility of participants screened under other GSK studies under identical testing conditions
6.3. Rescreening/Transfer (new section added)	Participants who were screen failure / withdrawn prior to T-cell administration may be rescreened in the same study/substudy or transferred to any applicable GSK-sponsored study or substudy of this protocol. Rescreening, leukapheresis procedure or manufacture process may be waived after consultation with Sponsor.	To allow for re-allocation of participants onto other suited protocols/substudies when available, and for the possibility of skipping steps that have already been completed under the original comparable protocol, after consultation with Sponsor.
8.1. Discontinuation of Study Intervention 8.1.1 Single Dose Administration	Introduced references for dose administration, safety assessment and monitoring, for reporting of AEs, and supportive care guidance. Included instructions for resuming infusion when infusion-related reaction Grade ≤2 resolved to Grade <1.	Added references for single dose administration and instructions for potential resuming conditions after infusion-related reaction.
8.2.3. Temporary Discontinuation	Addressing severe reactions associated with liver toxicities in between the 2 split doses infusion.	Clarification of instructions.
9.1.2. GSK Safety Review Team Mandated Study Pause Due to GBS	Paragraph on Mandated Study Pause Due to GBS removed because redundant with Section 8.5.	Removed redundancy.
9. Study Assessments and Procedures 9.1.5. Vital Signs	Clarified that blood pressure, pulse measurements, respiratory rate and body temperature should be assessed by institutional standards. Optimized wording to make the order of assessments between vital signs, EKG and blood draws a recommendation rather than a requirement.	Will allow sites to use local institutional guidance.
9.1.6 Cardiac Assessments	Addition of serum troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests	Addition of cardiac CCI tests as part of required baseline visit assessments

Section # and Name	Description of Change	Brief Rationale
CCI [redacted]		
9.2. Adverse Events and Serious Adverse Events	Updated definition of Delayed AEs to align with updated FDA guidance [FDA, 2020a]. Included Figure 3 Time Period for Collecting AE and SAE Information as visual aid to follow AE/SAE reporting instructions Clarify that AESIs will be reported to the Sponsor (Medical Monitor or designee) within 24 hours via e-mail (see SRM for further instructions.	Updated definitions of 6 categories of delayed AEs per FDA. Harmonized communication on AE/SAE collection. Clarification of AESI reporting instructions.
9.2.5. Pregnancy	Clarified contraception period duration to specify a minimum of 12 months from start of T-cell infusion. Included additional contraception requirements applicable to the use of fludarabine and cyclophosphamide chemotherapies. Added instruction to Investigator to advise participants on the conservation of sperm prior to initiating treatment. For participants who have persisting GSK3377794 beyond 12 months post infusion: once persistence test results show below level of detection for 2 consecutive times, Sponsor will notify the site that contraception period requirement is over.	Clarification of contraception requirements.
9.2.7 Adverse Events of Special Interest (AESIs)	Added instructions for Grade 3 or higher AESI of GvHD to be also reported as an SAE within 24 hours.	Updated instructions.

Section # and Name	Description of Change	Brief Rationale
9.3.1 Evaluation of Anti-Cancer Activity	Clarification that in cases where contrast enhanced CT is contraindicated, a Magnetic Resonance Imaging (MRI) of the abdomen/pelvis (with and without gadolinium contrast), and an MRI (with and without gadolinium contrast) or a non-contrast enhanced CT of the chest is acceptable.	Clarification of imaging modalities.
9.10.1. Tumor Biopsy	Clarification of time points for biopsy collections (Baseline, Week 4 and progression).	Wording optimization.
9.10.9. Genetic Blood Sample (section added)	Section added	Added clarification on genetic analysis plan.
10.4. Populations for Analyses	- Screened Population was amended to include "All participants who signed an ICF to participate in the study" - Enrolled and Intent-To-Treat (ITT) populations were amended to the same definition of "All participants who started leukapheresis procedure" - Modified Intent-To-Treat (mITT) population was amended to include "All participants who received any dose of NY-ESO-1 specific T cells"	Optimization and harmonization of Populations for analyses:at program level.
12.1.10 Remote Monitoring and Source Data Verification	Addition of provision that when onsite monitoring is not permissible due to site/local restrictions (such as with epidemic and/or pandemic), remote monitoring may be employed that ensures all of the following requirements are met	Clarification on remote monitoring.
12.2. Appendix 2: Clinical Laboratory Tests	Specified that for Clinical Chemistry BUN, both BUN or UREA tests are acceptable. Addition of Fibrinogen as part of the Coagulation test requirements Addition of Ferritin, serum troponin, NT-proBNP / BNP as part of the Other Tests.	Clarification of laboratory tests.
12.4.2 Contraception guidance	Added potential risks to fetus linked to treatment with fludarabine and cyclophosphamide. Added risk that cyclophosphamide treatment may result in partial or total sterility in male participants.	To clarify risks to fetus and to male sterility linked to treatment with lymphodepleting chemotherapy regimen in response to regulatory agency's request.

Section # and Name	Description of Change	Brief Rationale
12.7.5. Management of Cytokine Release Syndrome (CRS)	Addition of monitoring requirement for suspected CRS, with chemistry, hematology, ferritin, coagulation, C reactive protein, troponin and NT-proBNP / BNP labs. Addition of monitoring requirement on left ventricular ejection fraction for suspected CRS. Clarified posology for tocilizumab and alternative options for participants not responding to tocilizumab.	Additions of monitoring requirements for CRS according to SITC 2020 guideline on immune effector cell-related adverse events.
12.7.8. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Clarification that Brain MRI must be taken at screening and repeated at baseline if more than 4 months have elapsed between screening MRI and baseline. Addition of monitoring requirement for suspected ICANS, with chemistry, hematology, ferritin, coagulation, and C-reactive protein labs. Clarification of ICANS management table Addition that tocilizumab may worsen ICANS in some situations.	Clarification on Brain MRI requirements for reference assessments. Additions of monitoring requirements for ICANS according to SITC 2020 guideline on immune effector cell-related adverse events.
12.7.10. Management of Guillain-Barré Syndrome (GBS) 12.8 Appendix 8: Neurology Consultation – Further Guidelines for Signs and Symptoms Suggestive of Guillain-Barré Syndrome (new)	Added cross reference to new Appendix 8 for Neurology Consultation. Added Appendix 8 for further guidelines for Signs and Symptoms Suggestive of Guillain-Barré Syndrome (GBS)	To clarify diagnosis of GBS.
12.7.2.2 Herpex Simplex and Varicella Zoster and Epstein Barr virus (EBV) 12.7.2.4 Hepatitis B prophylaxis	Clarified that prophylaxis for herpex simplex and varicella zoster should be initiated prior to lymphodepletion. Clarified that additional considerations on Hepatitis B prophylaxis (acceptable regimens included) will be left to the Investigator's discretion in accordance with label recommendations and institutional guidelines.	To clarify Infection prophylaxis language.

Section # and Name	Description of Change	Brief Rationale
Substudy 1		
2. Schedule of activities Table 1. Substudy 1 Schedule of Activities – Screening and Leukapheresis	Footnote #1 (Table 1) has been amended to state that consent for Leukapheresis and Treatment must be repeated if given more than 90 days prior to leukapheresis procedure. Minor wording clarifications for footnotes #3, 5 and 8. Footnote #4 clarifies that optional Genetics sample "may be collected any time from signature of optional consent until leukapheresis". Footnote #9 clarifies that "CD3 count prior to leukapheresis should preferably be performed with 24 hours prior to leukapheresis procedure". Footnote #10 aligns with Core Protocol Section 9.1.5 on Vital Signs collection, allowing institutional standard methods for collection. Footnote #17 added to reference details of renal assessment in Substudy 1 Section 6.1 Table 9.	Clarification and alignment of SOA with other section changes

Section # and Name	Description of Change	Brief Rationale
2. Schedule of activities Table 2. Substudy 1 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment and Follow-up) And Table 4. Substudy 1 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment and Follow-up) for Split Dosing	Added standard method of conversion for calendar visit scheduling between month to week, and week to day. Combined Transgene Copies (Persistence for Safety) and CCI rows into one as only one sample will be collected to perform both tests. Footnote #16 clarified to instruct that "CT/MRI assessments only need to continue until confirmed PD". Added requirement for ferritin, troponin and NT-proBNP / BNP test prior to Lymphodepletion (Table 2) Added Coagulation assessments for baseline, Day 1 thru 4, Day 6, Day 8, and Day 15 (Table 2) Included requirement for suspected CRS or ICANS to monitor chemistry, hematology, ferritin, coagulation and C reactive protein labs, daily for a week then every other day until symptoms are improving or an alternative diagnosis is confirmed. Included requirement for monitoring of troponin and NT-proBNP / BNP labs for CRS grade≥2 as clinically indicated. Minor clarifications to footnote #33 to extend window of collection of genetic sample until first day of lymphodepletion and footnote #34 to clearly identify start of lymphodepletion day per indication.	Clarification and alignment of SOA with other section changes Addition of cardiac CCI and coagulation tests. Clarification of schedule of assessment for suspected CRS or ICANS. Clarification of SOA footnotes.
2. Schedule of activities Table 3. Substudy 1 Schedule of Activities – PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) And Table 5. Substudy 1 Schedule of Activities – PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) for Split Dosing	Clarified that Sample Type for dnTGF-βRII should be "whole blood" instead of PBMC. Removal of Day 64 since Week 10 visit is not showing on the table (per footnote #1). Updated Requirement for on-study biopsy at Week 4 instead of Week 6 (Footnote #9 specifies that the window of collection for the Week 4 biopsy is extended from Day 21 to Day 39). Corrected schedule of collection for Cytokine Analyses (removal of Week 5, 7 and 9 collections) Updated footnote #5 related to collection of cytokines when CRS is suspected, to reference local laboratory monitoring	Clarification and alignment of SOA with other section changes

Section # and Name	Description of Change	Brief Rationale
2. Schedule of activities Table 6. Substudy 1 Schedule of Activities – Follow-up after Disease Progression or after Completion of Interventional Phase Follow-up	Combined Transgene Copies (Persistence for Safety) and [redacted] rows into one as only one sample will be collected to perform both tests. Clarified language to align with Long-term Follow-up Study 208750, including: - Discontinuation of persistence [redacted] monitoring at ≥2 year post T-cell infusion for participants whose transduced T cells are undetected for 2 consecutive visit assessments - Allow medical evaluations to take place via telemedicine (e.g. phone call or video conferences) and/or home healthcare where country and/or local regulations allow - Added option of remote visits for years 6-15	Clarification and alignment of SOA with other section changes
3.2.1 Risk Assessment Table 7. Risk Mitigation Strategy	Corrected reference to IP as GSK3901961 for Substudy 1. Updated risk assessment table: - To include risks of decreased vision and peripheral neuropathy for lymphodepleting chemotherapy (fludarabine/cyclophosphamide); - To include/amend risks of haematopoietic cytopenias, hypersensitivity, reactivation of previous viral infections after prolonged leukopenia, neutropenia (including fatal neutropenia) decreased vision, to TCR-T infusion - To remove risk of pulmonary toxicity as it should only be specific to substudy 2.	Update to risk mitigation.

Section # and Name	Description of Change	Brief Rationale
4. Objectives and Endpoints	Reformatted Secondary Objectives and Endpoints into "Secondary – Efficacy" and "Secondary – Pharmacokinetics".	To clarify subcategories of secondary objectives.
	CCI [redacted]	
	Combined Frequency and severity of Adverse Events (AEs), Serious AEs (SAEs) and AEs of Special Interest (AESIs) as one single endpoint. Optimized description of Secondary – Pharmacokinetics objectives and endpoints. Updated list of abbreviations.	Standardization of reporting. Clarification of Pharmacokinetics plan. Finalization of table.
5.1.1. Dose Confirmation Phase And 6.1 Former Inclusion #10 (deleted) And 6.1 Former Inclusion #16 (now Inclusion #13) And 6.2 Former Exclusion #1 (deleted)	Cohort 1 metastatic NSCLC participants must have received prior to lymphodepletion (Inclusion #13) a PD-1/PD-L1 checkpoint blockade therapy "and, in the same or different line of treatment, a platinum containing chemotherapy, or participant is intolerant to it". Cohort 1 metastatic NSCLC participants arborring an actionable genetic aberration (e.g., BRAF, ALK/ROS1) per NCCN guidelines, must also have received prior to lymphodepletion (Inclusion #13) "the standard of care (SOC) targeted therapy as recommended by NCCN or equivalent country-level guidelines (e.g., ESMO, NICE)".	Clarification on disease characteristics for inclusion of Cohort 1 NSCLC participants. Removal of any requirement of specific anti-cancer treatment prior to leukapheresis.
5.1.1.1 Determining the R2PD	Minor clarification to the RP2D suggested dose which will have ≥6 participants treated at this dose and an observed toxicity rate ≤1/3.	Clarification of threshold for suggested RP2D dose.
5.1.3 Participant Journey	Optimization of wording to Participant journey description to align with equivalent Core Protocol Section 5.2.	Alignment of wording with equivalent Core protocol section

Section # and Name	Description of Change	Brief Rationale
5.1.4 Tumor Biopsies (new section added) And 6.1 Former Inclusion Criterion #5 (now Inclusion Criterion #3) 6.1 Inclusion Criterion #24	Added requirements for on-study tumor biopsies A representative tumor tissue specimen [archived or fresh biopsy] with associated pathology report should be available to perform NY ESO 1 antigen expression analysis unless an appropriate recent NY-ESO-1 expression result is already available. Clarification of requirements for baseline biopsy.	Clarification.
5.3 End of Substudy definition	Clarification of end of Interventional Phase and end of substudy for individual participants as well as for the entire substudy/cohort	Clarification of patient disposition
5.1 Overall Design 6.1 Inclusion Criteria 6.2 Exclusion Criteria	Optimization of Treatment Fitness and Eligibility criteria prior to Lymphodepletion	Removed requirement for repetition of all assessments for eligibility criteria that were already met prior to leukapheresis. Replaced by a Treatment Fitness assessment of the safety criteria in consultation with Medical Monitor.
6.1 Former Inclusion #6 moved to Inclusion #4	Clarification on translocation requirement for inclusion of SS participants (Cohort 2): Methods, such as, but not limited to, Fluorescence in situ hybridization (FISH) assay or Next Generation Sequencing (NGS) are commonly used to detect translocations.	Facilitate inclusion of SS participants on the basis of confirmed histology only.
6.1 Former Inclusion #3 moved to Inclusion #10 And Former Inclusion #4 moved to Inclusion #11 And 6.1 Former Inclusion #14 (now Inclusion #23)	Participants must have measurable disease by RECIST v1.1 (Inclusion #10) and evidence of radiographic or clinical disease progression only prior to leukapheresis (Inclusion #11). Participants must have documented radiographic evidence of disease progression from prior line of therapy prior to lymphodepletion (Inclusion #23).	Clarification on disease requirements to allow for participants who have not progressed to undergo Target Expression Screening.

Section # and Name	Description of Change	Brief Rationale
6.1 Former Inclusion #8 (deleted) And 6.1 Former Inclusion #15 (now Inclusion #12)	Cohort 2 advanced (metastatic or unresectable) SS participants must have completed at least one standard of care treatment including anthracycline containing regimen OR is intolerant to the therapy. Participants who are not candidates to receive doxorubicin should have received ifosfamide unless also intolerant to or ineligible to receive ifosfamide. Participants who received neoadjuvant/adjuvant anthracycline or ifosfamide based therapy and progressed within 6 months with metastatic disease will be eligible.	Clarification on disease characteristics for inclusion of SS participants.
6.1 Former Inclusion #18 (now Inclusion #15)	Participants must have a predicted life expectancy that is ≥6 months (Inclusion #15)	Extension of projected life expectancy requirement because leukapheresis can now be performed earlier in treatment plan.
6.1 Former Inclusion #19 (now Inclusion #16)	Participants must have a Left ventricular ejection fraction ≥45% with no evidence of clinically significant pericardial effusion or as per institution's guidelines (Inclusion #16)	Clarification.

Section # and Name	Description of Change	Brief Rationale
6.1 Former Inclusion #20 (now Inclusion #18) Table 9.	Participant must have adequate organ function and blood cell counts within 7 days prior to the day of leukapheresis, (or first day of lymphodepletion during Treatment fitness assessment), as indicated by the laboratory values in Table 9 (Inclusion #18 Clarification of Definitions of Adequate Organ Function: - ANC (must be obtained without G-CSF support) - CD3 count is no more an eligibility criterion - Platelets must be ≥100 x10^9/L - Renal function has been clarified based on participant age, and method - Albumin must be ≥3.5 g/dL - Footnote a) prohibits platelet transfusions accepted within 14 days from testing - Footnote b) prohibits red blood cell transfusions to meet minimum hematologic values for eligibility - Footnote c) clarifies reassessment conditions prior to lymphodepletion - Footnote d) references guideline on anticoagulant medication prior to lymphodepletion	Clarification.
6.1 Former Inclusion Criterion #21 (now Inclusion #19)	Clarify that contraception for male and female participants must be followed during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or until persistence of gene modified cells in the participant's blood is below the level of detection for 2 consecutive assessments, whichever is longer.	Clarification.
6.2 Exclusion Criteria 6.2.2 Leukapheresis Eligibility Screening And 6.2.3 Treatment And Table 10 – Washout periods	Clarification of washout periods requirements prior to leukapheresis and prior to lymphodepletion.	Alignment with cell gene therapy program.

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria Former Exclusion Criterion #2 (now Exclusion criterion #6) And Exclusion criterion #5 (deleted)	 Clarification of CNS metastases exceptions for NSCLC participants. Removed restriction on maximum lines of therapy for NSCLC participants (former Exclusion criterion #5).	Broaden NSCLC patient eligibility
6.2 Former Exclusion Criteria #6 and 7 (now Exclusion criteria #3 and 4)	Per Section 6.3.5: - Added exception to exclusion of participants who have received prior genetically engineered NY-ESO-1 specific T cells, NY-ESO-1 vaccine or targeting antibody. - Added exception to participants who have received prior gene therapy using an integration vector.	Allow participants who have benefited from GSK3377794 (lete-cel) to be considered for treatment with GSK3901961 under conditions defined in Section 6.3.5.
6.3.4. Rescreening/Transfer (new section added)	Participants who were screenfailure/withdrawn prior to T-cell administration may be rescreened in the same study/substudy or transferred to any applicable GSK-sponsored study or substudy of this protocol. Rescreening, leukapheresis procedure or manufacture process may be waived after consultation with Sponsor.	To allow for re-allocation of participants onto other suited protocols/substudies when available, and for the possibility of skipping steps that have already been completed under the original comparable protocol, after consultation with Sponsor.
6.3.5. Potential eligibility of participants who have previously received letetresgene autoleucel	Participants who achieved a confirmed response of CR or PR or SD ≥3 months following first infusion of GSK3377794 (lete-cel) could possibly benefit post progression from receiving a second course of treatment with next generation NY-ESO-1 specific T cells (such as GSK3901961). Considerations will be made on a case by case basis. Rationale and minimal requirements are laid out in this section	To allow for possible future inclusion of prior lete-cel treated participants.
7.1.2 Bridging Therapy and/or Intermediate Standard of Care Anti-Cancer of Therapy before Lymphodepletion	Clarified that bridging or standard of care systemic chemotherapy, experimental therapy and/or local therapy may be administered between Target Expression Screening and Leukapheresis; and systemic chemotherapy may be administered, between Leukapheresis and the start of Lymphodepletion, if a participant has progressive disease and cannot be treatment-free.	Added clarification.

Section # and Name	Description of Change	Brief Rationale
7.1.3 Lymphodepleting Chemotherapy	Clarified situations where Medical Monitor must be consulted to discuss Lymphodepleting regimen dose adjustments. Clarified that if creatine clearance is estimated that the same method as for adequate organ function should be used to consider fludarabine dose adjustments Clarified requirement for timing of G-CSF start post last chemotherapy dose.	Added safety oversight and precautions. Added clarification.
7.5.1 Prohibited Concomitant Medication and Treatment	Removal of redundant sentence prohibiting use of any non-protocol antineoplastic therapy.	Added clarifications.
7.5.2 Permitted Concomitant Medication and Treatment	Added recommendations for participants on therapeutic anticoagulants	Added clarification.
7.5.3 Rescue Medications and Supportive Care	Minor optimization of language	Added clarifications.
7.6 Dose Modification	Addition of standard language on provision for additional manufacturing from excess banked leukapheresis product or for a second leukapheresis if the transduced cell dose does not meet the minimum dose required.	Added clarifications.
9.1 Dose Selection Committee	Addition of language to cover situation where DLTs are observed	Added clarifications.
10.1.1 Modified Toxicity Probability Interval 2 (mTPI-2) Based Dose Confirmation Design	Minor clarification to the RP2D suggested dose which will have ≥6 participants treated at this dose and an observed toxicity rate ≤1/3.	Added clarifications.

Section # and Name	Description of Change	Brief Rationale
Substudy 2		
2. Schedule of activities Table 1. Substudy 2 Schedule of Activities – Screening and Leukapheresis	Footnote #1 (Table 1) has been amended to state that consent for Leukapheresis and Treatment must be repeated if given more than 90 days prior to leukapheresis procedure. Minor wording clarifications for footnotes #3, 5 and 7. Footnote #4 clarifies that optional Genetics sample "may be collected any time from signature of optional consent until leukapheresis". Footnote #8 clarifies that "CD3 count prior to leukapheresis should preferably be performed within 24 hours prior to leukapheresis procedure". Footnote #9 aligns with Core Protocol Section 9.1.5 on Vital Signs collection, allowing institutional standard methods for collection. Footnote #16 added to reference details of renal assessment in Substudy 2 Section 6.1 Table 10.	Clarification and alignment of SOA with other section changes
2. Schedule of activities Table 2. Substudy 2 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment and Follow-up) And Table 4. Substudy 2 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment and Follow-up) for Split Dosing	Added standard method of conversion for calendar visit scheduling between month to week, and week to day. Combined Transgene Copies (Persistence for Safety) and CCI rows into one as only one sample will be collected to perform both tests. Footnote #15 clarified to instruct that "CT/MRI assessments only need to continue until confirmed PD". Added requirement for ferritin, troponin and NT-proBNP / BNP test prior to Lymphodepletion (Table 2) Added Coagulation assessments for baseline, Day 1 thru 4, Day 6, Day 8, and Day 15 (Table 2) Included requirement for suspected CRS or ICANS to monitor chemistry, hematology, ferritin, coagulation and C reactive protein labs, daily for a week then every other day until symptoms are improving or an alternative diagnosis is confirmed. Included monitoring of troponin and NT-proBNP / BNP labs for CRS grade ≥2 as clinically indicated.	Clarification and alignment of SOA with other section changes Addition of cardiac CCI and coagulation tests. Clarification of schedule of assessment for suspected CRS or ICANS. .

Section # and Name	Description of Change	Brief Rationale
2. Schedule of activities Table 3. Substudy 2 Schedule of Activities – PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) And Table 5. Substudy 2 Schedule of Activities – PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) for Split Dosing	Clarified that Sample Type for dnTGF-βRII should be "whole blood" instead of PBMC. Removal of Day 64 since Week 10 visit is not showing on the table (per footnote #1). Updated Requirement for on-study biopsy at Week 4 instead of Week 6 (Footnote #8 specifies that the window of collection for the Week 4 biopsy is extended from Day 21 to Day 39). Corrected schedule of collection for Cytokine Analyses (removal of Week 5, 7 and 9 collections) Updated footnote related to collection of cytokines when CRS is suspected to reference local laboratory monitoring	Clarification and alignment of SOA with other section changes
2. Schedule of activities Table 6. Substudy 2 Schedule of Activities – Follow-up after Disease Progression or after Completion of Interventional Phase Follow-up	Combined Transgene Copies (Persistence for Safety) and CCI rows into one as only one sample will be collected to perform both tests. Clarified language to align with Long-term Follow-up Study 208750, including: - Discontinuation of persistence CCI monitoring at ≥2 year post T-cell infusion for participants whose transduced T cells are undetected for 2 consecutive visit assessments - Allow medical evaluations to take place via telemedicine (e.g. phone call or video conferences) and/or home healthcare where country and/or local regulations allow - Added option of remote visits for years 6-15	Clarification and alignment of SOA with other section changes
3.2.1 Risk Assessment Table 7. Risk Mitigation Strategy	Corrected reference to IP as GSK3845097 for Substudy 2. Updated risk assessment table: - To include risks of decreased vision and peripheral neuropathy for lymphodepleting chemotherapy (fludarabine/cyclophosphamide); - To include/amend risks of haematopoietic cytopenias, hypersensitivity, reactivation of previous viral infections after prolonged leukopenia, neutropenia (including fatal neutropenia) decreased vision, to TCR-T infusion.	Update to risk mitigation.

Section # and Name	Description of Change	Brief Rationale
4. Objectives and Endpoints	Reformatted Secondary Objectives and Endpoints into "Secondary – Efficacy" and "Secondary – Pharmacokinetics".	To clarify subcategories of secondary objectives.
	CCI [redacted]	
	Combined Frequency and severity of Adverse Events (AEs), Serious AEs (SAEs) and AEs of Special Interest (AESIs) as one single endpoint. Optimized description of Secondary – Pharmacokinetics objectives and endpoints. Updated list of abbreviations.	Standardization of reporting. Clarification of Pharmacokinetics plan. Finalization of table.
5.1.1.1 Determining the R2PD	Minor clarification to the RP2D suggested dose which will have ≥6 participants treated at this dose and an observed toxicity rate ≤1/3.	Clarification of threshold for suggested RP2D dose.
5.1.3 Participant Journey	Optimization of wording to Participant journey description to align with equivalent Core Protocol Section 5.2.	Alignment of wording with equivalent Core protocol section
5.1.4 Tumor Biopsies (new section added)And 6.1 Former Inclusion Criterion #5 (now Inclusion Criterion #4) 6.1. Former Inclusion criterion # 21 (now inclusion Criterion #24)	Added requirements for on-study tumor biopsies A representative tumor tissue specimen [archived or fresh biopsy] with associated pathology report should be available to perform NY ESO 1 antigen expression analysis unless an appropriate recent NY-ESO-1 expression result is already available. Clarification of requirements for baseline biopsy.	Clarification.
5.3 End of Substudy definition	Clarification of end of Interventional Phase and end of substudy for individual participants as well as for the entire substudy/cohort	Clarification of patient disposition
5.1 Overall Design 6.1 Inclusion Criteria 6.2 Exclusion Criteria	Optimization of Treatment Fitness and Eligibility criteria prior to Lymphodepletion	Removed requirement for repetition of all assessments for eligibility criteria that were already met prior to leukapheresis. Replaced by a Treatment Fitness assessment of the safety criteria in consultation with Medical Monitor.

Section # and Name	Description of Change	Brief Rationale
6.1 Former Inclusion #3 moved to Inclusion #9 And Former Inclusion #4 moved to Inclusion #10 And 6.1 Former Inclusion #12 (now Inclusion #19)	Participants must have measurable disease by RECIST v1.1 (Inclusion #9) and evidence of radiographic or clinical disease progression only prior to leukapheresis (Inclusion #10). Participants must have documented radiographic evidence of disease progression from prior line of therapy prior to lymphodepletion (Inclusion #19).	Clarification on disease requirements to allow for participants who have not progressed to undergo Target Expression Screening..
6.1 Former Inclusion #6 moved to Inclusion #4	Clarification on translocation requirement for inclusion of SS participants: Methods, such as, but not limited to, Fluorescence in situ hybridization (FISH) assay or Next Generation Sequencing (NGS) are commonly used to detect translocations.	Facilitate inclusion of SS participants on the basis of confirmed histology only.
6.1 Former Inclusion #8 (deleted) And 6.1 Former Inclusion #13 (now Inclusion #11)	Advanced (metastatic or unresectable) SS participants must have completed at least one standard of care treatment including anthracycline containing regimen OR is intolerant to the therapy. Participants who are not candidates to receive doxorubicin should have received ifosfamide unless also intolerant to or ineligible to receive ifosfamide. Participants who received neoadjuvant/adjuvant anthracycline or ifosfamide based therapy and progressed within 6 months with metastatic disease will be eligible.	Clarification on disease characteristics for inclusion of Cohort 2 SS participants.
6.1 Former Inclusion #15 (now Inclusion #13)	Participants must have a predicted life expectancy that is ≥6 months (Inclusion #13).	Extension of projected life expectancy requirement because leukapheresis can now be performed earlier in treatment plan.
6.1 Former Inclusion #16 (now Inclusion #14)	Participants must have a Left ventricular ejection fraction ≥45% with no evidence of clinically significant pericardial effusion or as per institution's guidelines (Inclusion #14).	Clarification.

Section # and Name	Description of Change	Brief Rationale
6.1 Former Inclusion #18 (now Inclusion #16) Table 10.	Participant must have adequate organ function and blood cell counts within 7 days prior to the day of leukapheresis, (or first day of lymphodepletion during Treatment fitness assessment), as indicated by the laboratory values in Table 10 (Inclusion #16 Clarification of Definitions of Adequate Organ Function: - ANC (must be obtained without G-CSF support) - CD3 count is no more an eligibility criterion - Platelets must be ≥100 x10^9/L - Renal function has been clarified based on participant age, and method - Albumin must be ≥3.5 g/dL - Footnote a) prohibits platelet transfusions accepted within 14 days from testing - Footnote b) prohibits red blood cell transfusions to meet minimum hematologic values for eligibility - Footnote c) clarifies reassessment conditions prior to lymphodepletion - Footnote d) references guideline on anticoagulant medication prior to lymphodepletion	Clarification.
6.1 Former Inclusion Criterion #19 (now Inclusion #17)	Clarify that contraception for male and female participants must be followed during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or until persistence of gene modified cells in the participant's blood is below the level of detection for 2 consecutive assessments, whichever is longer.	Clarification.
6.2 Exclusion Criteria 6.2.2 Leukapheresis Eligibility Screening And 6.2.3 Treatment And Table 11 – Washout periods	Clarification of washout periods requirements prior to leukapheresis and prior to lymphodepletion.	Alignment with cell gene therapy program.

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria Former Exclusion Criterion #1 (now Exclusion criterion #6)	Move CNS metastases requirement to prior Leukapheresis	Optimization of screening for eligibility
6.2 Exclusion Criteria #3 and 4	Per Section 6.3.5: - Added exception to exclusion of participants who have received prior genetically engineered NY-ESO-1 specific T cells, NY-ESO-1 vaccine or targeting antibody. - Added exception to participants who have received prior gene therapy using an integration vector.	Allow participants who have benefited from GSK3377794 (lete-cel) to be considered for treatment with GSK3901961 under conditions defined in Section 6.3.5.
6.3.4. Rescreening/Transfer (new section added)	Participants who were screenfailure/withdrawn prior to T-cell administration may be rescreened in the same study/substudy or transferred to any applicable GSK-sponsored study or substudy of this protocol. Rescreening, leukapheresis procedure or manufacture process may be waived after consultation with Sponsor.	To allow for re-allocation of participants onto other suited protocols/substudies when available, and for the possibility of skipping steps that have already been completed under the original comparable protocol, after consultation with Sponsor.
6.3.5. Potential eligibility of participants who have previously received letetresgene autoleucel	Participants who achieved a confirmed response of CR or PR or SD ≥3 months following first infusion of GSK3377794 (lete-cel) could possibly benefit post progression from receiving a second course of treatment with next generation NY-ESO-1 specific T cells (such as GSK38445097). Considerations will be made on a case by case basis. Rationale and minimal requirements are laid out in this section	To allow for possible future inclusion of prior lete-cel treated participants.
7.1.2 Bridging Therapy and/or Intermediate Standard of Care Anti-Cancer of Therapy before Lymphodepletion	Clarified that bridging or standard of care systemic chemotherapy, experimental therapy and/or local therapy may be administered between Target Expression Screening and Leukapheresis; and systemic chemotherapy may be administered, between Leukapheresis and the start of Lymphodepletion, if a participant has progressive disease and cannot be treatment-free.	Added clarification.

Section # and Name	Description of Change	Brief Rationale
7.1.3 Lymphodepleting Chemotherapy	Clarified situations where Medical Monitor must be consulted to discuss Lymphodepleting regimen dose adjustments. Clarified that if creatine clearance is estimated that the same method as for adequate organ function should be used to consider fludarabine dose adjustments Clarified requirement for timing of G-CSF start post last chemotherapy dose.	Added safety oversight and precautions. Added clarification.
7.5.1 Prohibited Concomitant Medication and Treatment	Removal of redundant sentence prohibiting use of any non-protocol antineoplastic therapy.	Added clarifications.
7.5.2 Permitted Concomitant Medication and Treatment	Added recommendations for participants on therapeutic anticoagulants	Added clarification.
7.5.3 Rescue Medications and Supportive Care	Minor optimization of language	Added clarifications.
7.6 Dose Modification	Addition of standard language on provision for additional manufacturing from excess banked leukapheresis product or for a second leukapheresis if the transduced cell dose does not meet the minimum dose required.	Added clarifications.
9.1 Dose Selection Committee	Addition of language to cover situation where DLTs are observed	Added clarifications.
10.1.1 Modified Toxicity Probability Interval 2 (mTPI-2) Based Dose Confirmation Design	Minor clarification to the RP2D suggested dose which will have ≥6 participants treated at this dose and an observed toxicity rate ≤1/3.	Added clarifications.
Throughout document	Minor edits and typo corrections done	Editorial changes

13.2. Amendment 2 (04 November 2021)

Overall Rationale for Amendment 2:

1. Implementation of additional safety monitoring measures in accordance with a recent Dear Investigator Letter and safety events.

2. For participants treated as of protocol amendment 2, the cyclophosphamide dose in the lymphodepleting chemotherapy was reduced on Day -7 thru Day -4 to further optimize and reduce potential for acute and prolonged cytopenias while also minimizing impact on efficacy.

3. For NSCLC participants in Substudy 1 Cohort 2 treated as of Protocol Amendment 2, the lymphodepleting chemotherapy schedule was changed from Day -8 through Day -5 to Day -7 through Day -4 to align with the schedule for the sarcoma participant cohort.

4. Inclusion of myxoid/round cell liposarcoma (MRCLS) as a second translation-related sarcoma indication.

Section # and Name	Description of Change	Brief Rationale
Core protocol		
1 Synopsis – Rationale	Updated IB cutoff date and number of patients treated with lete-cel	Added most recent IB data
1 Synopsis - Overall design	Description of substudies moved to Section 12.12, Reference to Section 12.12 for further details regarding additional substudies.	In anticipation of additional substudies, enables administrative changes to document.
Synopsis Screening and Section 5.2 Screening	Addition of LAGE-1a as potential antigen assay	Inclusion of LAGE-1a as potential screen for antigen testing to expand potential participant eligibility
3 Introduction	Reference to Secction 12.12 for details regarding substudies	In anticipation of additional substudies, enables administrative changes to document.
3.2.2 GSK3377794 (letetresgene autoleucel, lete-cel) (lete-cel)	Updated lete-cel IB details	Added most recent IB data
3.2.2 GSK3377794 (letetresgene autoleucel, lete-cel) (lete-cel)	Updated LTFU study 208750 details	Study 208570 is not product specific
3.2.3 Next Generation Engineering	Reference to Section 12.12 for details regarding substudies	In anticipation of additional substudies, enables administrative changes to document.
1 Synopsis Next Generation Engineering	Added MRCLS to figure for Substudy 1 and Substudy 2	Inclusion ofMRCLS in both substudies
5.1 Overall design	Updated study schema	Inclusion of MRCLS in both substudies

Section # and Name	Description of Change	Brief Rationale
5.1 Overall design	Reference to Section 12.12 for details regarding substudies	In anticipation of additional substudies, enables administrative changes to document.
5.2 Participant Journey	Included reference to substudies for HLA testing substudy specific details	HLA testing is substudy specific – details are not provided in Core but in individual substudy sections.
5.2 Participant Journey Part 1 Screening	Included third option of target expression screening	Added option of proceeding with tumor sample collection based on a positive local HLA result..
5.3 Number of Participants	Reference to Section 12.12 for details regarding substudies	In anticipation of additional substudies, enables administrative changes to document.
6.2 Screening Under Other GSK Studies	Updated to indicate acceptability of LAGE-1a positive participants	In order to accommodate participants from other studies whose tumor was positive for LAGE-1a and to facilitate study-to-study transfer of these participants
6. Protocol population	Added sentence to refer to substudies for protocol population details relevant to each substudy.	Transition to modular format.
8.1.2 Split Dose Administration	Updated language to refer to substudies for split dosing	Transition to modular format
8.2 Dose Limiting Toxicity	Updated timing for DLT window for point 7 to harmonize	Typo correction
8.2 Dose Limiting Toxicity	Included reference to substudies for any substudy specific DLTs	In the event DLTs specific to a substudy arise, these will be added to the substudy via amendment
8.5 Study Stopping and Pausing Rules	Added reference to substudy for any specific safety assessments	In the event substudy specific safety assessments arise, these will be added to the substudy via amendment
9.1.6 Cardiac assessments	Added text to define specific cardiovascular risk factors and steps necessary to evaluate and monitor participant	Implementation of additional safety monitoring measures in accordance with a recent Dear Investigator Letter (21 Oct 2021)and safety events..
9.1.7 Pulmonary Assessments	Added new section on participant pulmonary function assessment prior to lymphodepletion	Implementation of additional safety monitoring measures in accordance with a recent Dear Investigator Letter (21 Oct 2021) and safety events.
9.1.8 Monitoring for Immune Effector Cell-Associated Neurotoxicity Syndrome	Added reference to substudy for any specific assessments	Added language in the event there are additional assessments specific to a substudy.
9.1.9 Monitoring for Demyelinating Neuropathy and other Neurological Events	Added reference to substudy for any specific assessments	Added language in the event there are additional assessments specific to a substudy.

CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Updated timing for AE and SAE collection	Clarified AE and SAE reporting guidance
9.2.5 Pregnancy	Moved table of contraception use timings to Section 12.4 Contraception Guidance and Collection of Pregnancy Information	Added table of contraception use timings to appendix pertaining to contraceptive guidance rather than retain in the Pregnancy section
9.2.7 Adverse Events of Special Interest (AESIs)	Added reference to substudy for any specific assessments	Added language in the event there are additional assessments specific to a substudy.
9.8 Genetics	Clarified language and cross referenced Section 9.10	Streamlined language
CCI [redacted]		
9.10.1 Tumor Biopsy	Removal of time limitations and reference to substudy for archival tissue time limitations Formatted section by time of biopsy Included requirements on sample suitability	Indications vary by substudy Divided text into Screening, Baseline and On-study sampling times to enhance reader understanding Added guidance on type of biopsy that is acceptable per protocol
9.10.2 Liquid Bopsies (from circulating blood)	Included additional descriptive text	Added text to provide more background to research purpose of liquid biopsies
9.10.4 Cell Phenotype and Functional Activity	Included text about apheresis product	Expanded applicability of assays to both apheresis and manufactured product
9.10.5 dnTGFbRII Receptor Expression Analyses	Updated language to refer to substudies for dnTGFbRII Receptor Expression Analyses testing requirements	dnTGFbRII Receptor Expression Analyses are not tested in all substudies
9.10.8 Stool Collection for Microbiome Analysis	Deleted section	Removed because assay not being conducted under Protocol Amendment 2
11. References	Updated references section	Updated references to be core-specific
12.7 Appendix 7: Supportive Care Guidance	Included language to refer to substudy for additional substudy specific guidance, when applicable.	Added language in the event there are additional assessments specific to a substudy.
12.7.2 Infection	Included guidance for participants with indwelling central lines	Added guidance for increased monitoring of indwelling catheter lines to watch for infection

Section # and Name	Description of Change	Brief Rationale
12.7.2.6 Other Anti-Microbial Prophylaxis/Treatment	Included guidance for participants with severe or gross hematuria Included guidance for participants requiring anti-microbial therapy with cardiac toxicity risk	Added guidance to check for BK viruria and viremia. In adiditon, added guidance to raise site's awareness of need to carry out increased cardiac monitoring in participants receiving any anti-microbial agent with a recognized cardiac toxicity risk.
12.7.3 Hematologic and Blood Product Support	Included language for management of thrombocytopenia in in- and out-patient setting	Clarified out-patient support for completeness.
12.7.5 Management of Cytokine Release Syndrome	Included language for additional monitoring of participants with cardiac risks	Provided detailed guidance for monitoring of participants with cardiac risk factors who also develop CRS in an effort to minimize further risks.
12.11 Appendix 11: Abbreviations and Trademarks	Updated abbreviations list	Removed abbreviations no longer applicable
12.12. Appendix 12: List of substudies	Table of substudies added	Transition to modular format to enable administrative changes and provide overview of all substudies
13. Protocol Amendment History	Amendment 1 rationale and table moved to new section (Appendix 13)	Introduction of additional amendment.
Throughout document	Minor edits and type corrections done	Editorial changes
Table of contents	Udpated to refer only to Core	In an effort to support future modularization of the 209012 protocol, the Table of Contents was updated to reflect only the Core section of the protocol.
Section 11 References	Updated to include only those references relevant to the Core section of the protocol.	In an effort to support future modularization of the 209012 protocol, reference list was updated to include only those references relevant to the Core section of the protocol.

13.3. Amendment 3 (20 December 2021)

Overall Rationale for Amendment 3:

The three primary reasons for Amendment 3 are as follows:

- Substantial: Addition of Substudy 3 as "GSK4427296 [NYESO 1(c259) TCR engineered T cells using the Epi-R manufacturing process] in previously treated (2L+) HLA-A*02+ participants with NYESO 1+ and/or LAGE1a+ advanced SS or MRCLS" with a planned sample size of 19 and to be conducted in the United States only.

- Non-substantial: Splitting of master protocol into individual separate documents while organization of the sections does not change:
  1) The Core Master protocol captures the common design and supporting documentation, including an updated list of substudies and the history of amendments, and 2) Each substudy is included as an individual document.

- Non-substantial:Minor changes to Substudy 1 and 2 to ensure alignment of design and procedures across 3 substudies.

Section # and Name	Description of Change	Brief Rationale
Core		
1 Synopsis - Overall design	Reference to Section 12.12 for further details regarding additional substudies and planned overall sample size.	Inclusion of reference to master protocol planned overall sample size.
9.9 Immunogenicity Assessments	Specific asset references removed.	Specific reference removed as collections and assessments are intended to apply to any assets under current and future substudies.
12.2 Appendix 2: Clinical Laboratory Tests	Updated Note under table of Clinical Laboratory Tests mention LAGE-1a expression.	Inclusion of LAGE-1a tests results when applicable.
12.12. Appendix 12: List of substudies (updated)	Included Substudy 3 as "GSK4427296 [NYESO 1(c259) TCR engineered T cells using the Epi-R manufacturing process] in previously treated (2L+) HLA-A*02+ participants with NYESO 1+ and/or LAGE1a+ advanced SS or MRCLS" with a planned sample size of 19 and to be conducted in the United States only. Included master protocol overall planned sample size of approximately 67. Countries where substudy will be active is added for all 3 substudies	Inclusion of new substudy and update of overall estimated sample size.

Section # and Name	Description of Change	Brief Rationale
12.13. Appendix 13: Master Protocol Document History (new)	Table captures the chronology of each amendment, lists the documents that have been updated (including their document reference numbers), and identifies the current version for each individual document as component of the master protocol.	T Capture of history of protocol and document amendments before and after splitting of master protocol into individual separate documents (one for the core and one for each substudy).
Throughout document	Minor edits and typo corrections done	Editorial changes

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