Protocol Amendment 6

Study ID: 208467

Main Study Title: Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1-Specific (c259) T Cells, Alone or in Combination With Other Agents, in HLA-A2+ Participants With NY-ESO-1 and/or LAGE-1a Positive Solid Tumors (IGNYTE-ESO)

Sub-study 1 Title: Evaluation of Safety and Antitumor Activity of Lete-Cel (GSK3377794) in HLA-A2+ Participants With NY-ESO-1 Positive Previously Untreated Advanced (Metastatic or Unresectable) Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

NCT ID for Sub-study 1: NCT05993299

Date of Document: 04-NOV-2021

TITLE PAGE

Protocol Title: Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1-Specific (c259) T Cells, alone or in combination with other agents, in HLA-A2+ Participants with NY-ESO-1 and/or LAGE-1a Positive Solid Tumors (IGNYTE-ESO)

Protocol Number: 208467/Amendment 6

Compound Number: GSK3377794 (letetresgene autoleucel, lete-cel)

Short Title: Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered T Cells in NY-ESO-1 and/or LAGE-1a Positive Solid Tumors

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND Number: 18944

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Approval Date: 04-NOV-2021

SPONSOR SIGNATORY:

Protocol Title: Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1-Specific (c259) T Cells, alone or in combination with other agents, in HLA-A2+ Participants with NY-ESO-1 and/or LAGE-1a Positive Solid Tumors (IGNYTE-ESO)

Protocol Number: 208467/Amendment 6

Compound Number or Name: GSK3377794 (letetresgene autoleucel, lete-cel)

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

The signed page is a separate document.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 6	04-NOV-2021	TMF-14132897
Amendment 5	19-MAY-2021	TMF-13778474
Amendment 4	03-DEC-2020	2018N385677_07
Amendment 3	06-APR-2020	2018N385677_05
Amendment 2	05-FEB-2020	2018N385677_03
Amendment 1	21-JUN-2019	2018N385677_01
Original Protocol	05-Apr-2019	2018N385677_00

Amendment 6 - Date 04-NOV-2021

Overall Rationale for Amendment 6:

The primary rationale for protocol Amendment 6 is:

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

2. An increase in the number of participants in Substudy 2 from 70 planned to 87 participants (with 72 expected to receive the intended commercial drug product supply) was made to ensure greater statistical power for the purpose of registration.

3. For participants treated as of protocol amendment 6, 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.

4. For participants treated as of protocol amendments 6, the upper end of the target dose range of transduced T cells was increased from to 8×10^9 to 15×10^9 in order to maximize the delivery of cells for participants whose manufacture yields $>8\times10^9$ transduced T cells.

Section # and Name	Description of Change	Brief Rationale
Core protocol		
Synopsis	Number of participants was updated as per Core Section 5.2	This revision was made for consistency across sections
Synopsis	'Key decisions' was changed to 'key recommendations' of IDMC as per Core Section 5.4.1	This revision was made for consistency across sections
5.1 Overall Design	The note under Part 1: Screening was updated to align with changes made to the text in Section 6.3.	This revision was made for consistency across sections in the core and substudy sections of the protocol.
5.1 Overall Design	The window for pre-treatment tumor biopsy prior to initiating lymphodepletion was removed from the Core section Part 3: Lymphodepletion/Treatment, as it may be different for each substudy.	This revision was made to correct a discrepancy between window requirements for biopsy in the Core section (originally 28 days) and in substudy 1 (allowed to be 90 days for the 1L indication).
5.1 Overall Design	A window of "no sooner than 90 days post T-cell infusion" was added for patients entering a separate long-term follow-up protocol.	This window will allow the capture of adequate safety information after the T-cell infusion.
5.2 Number of Participants	The total planned participant numbers were changed from 80 to 97: Planned participant numbers in Substudy 2 changed from 70 to 87 Planned participant number to receive intended commercial drug product supply changed from 55 to 72 The planned participant number to ensure receive letetresgene changed from 45 to 60 A sentence was added stating that an additional 20% enrollment is factored in between leukapheresis and dosing.	The substudy 2 sample size was increased to ensure greater statistical power.
5.4.1 Data Monitoring Committee	'Key decisions' was changed to 'key recommendations' of IDMC	This revision was to align with IDMC charter wording.
6.1 Screen Failures	Collection of data may include disease characteristics, prior lines of anti cancer treatment, performance status and any serious adverse events (SAEs).	This revision was made to clarify collection of data on screenfailed participants
6.3 Screening Under Other GSK Studies (new section)	This section was added to indicate that 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.	This revision was to allow for target expression eligibility of participants screened under other GSK studies under identical testing conditions

Section # and Name	Description of Change	Brief Rationale
9.3.6 Cardiac Assessments	This section was revised to include a definition of participants with increased burden of cardiovascular risk, and for those identified patients to mandate a cardiologist consult prior to lymphodepletion and continuous cardiac telemetry for a minimum of 3 days post T-cell infusion.	This revision was made to mitigate cardiac complications in participants with high risk factors
9.3.7 Pulmonary Assessments (New Section)	This section recommends pulmonary consultation for any participant with any history or known lung metastases. Also closer monitoring is recommended for at least 3 days post T-cell infusion and in case of suspected CRS and should include frequent chest radiograms, fluid balance monitoring and continuous cardiac telemetry. Participants with compromised airway should be assessed prior to lymphodepletion (consider speech and swallow evaluation, as well as anaesthesia consult)	This section was added to recommend pulmonary assessments for participants with known lung metastases (active or previously treated)
9.3.12 Testing for Persistence of Transduced T cells and Insertional Oncogenesis	Participants with a persistence of transduced T cells >1% PBMCs and who have already been tested for Integration Site Analysis with a result of 'polyclonal', will only be retested if: persistence of transduced T cells has suddenly increased; OR in case of suspected/reported hematological maligancy	This revision was to clarify conditions for monitoring and retesting of participants who have already been tested for Integration Site Analysis with a result of 'polyclonal'
9.9 Biomarkers	A sentence was added concerning immune cell phenotyping to be assessed in the apheresis material, manufactured product, and post infusion blood samples.	This revision was to clarify the testing and to align with an addition in Section 9.9.4
9.9.1 Tumor biopsy	List of planned research studies to be performed with tumor biopsies was rearranged for better clarity on intent.	This revision was made to clarify the list of planned research studies
9.9.2 Liquid Biopsies (from circulating blood)	Removal of circulating cell-free RNA (cf-RNA) from list of biological entities to be extracted from liquid biopsies	Assay deprioritized to reduce amounts of blood collected.
9.9.4 Cell Phenotype and Functional Activity	Text was added to include the apheresis (starting material) in the planned testing.	This revision was to clarify of the materials to be tested.
Previous 9.9.8 Stool Collection for Microbiome analysis (Section deleted)	Removal of plan to collect stool sample to assess gut microbial community	Assay deprioritized.

Section # and Name	Description of Change	Brief Rationale
9.9.8 Genetic Blood Sample (formerly 9.9.9)	The association of candidate or genome-wide genetic variants may be explored with efficiacy (ORR) and safety such as but not limited to cytokine release syndrome frequency/severity/duration.	Harmonized language to central wording on genetic analyses.
12.7.2 Infection	For participants with indwelling central lines, consider increased surveillance to monitor for catheter-associated infections.	This revision was made to add recommendation to monitor for catheter-associated infections
12.7.2.6 Other Anti-Microbial Prophylaxis/Treatment	If a participant requires anti-microbial treatment associated with risk of cardiac toxicity, consider close monitoring of cardiac function (Section 9.3.6).	This revision was made to add recommendation to monitor for cardio toxicity associated with any anti-microbial treatment.
12.7.3 Hematologic and Blood Product Support.	Blood product support should be provided to maintain platelets >20 x 10^9/L in the out-patient setting.	This revision was made to clarify recommendation for blood product on participants in out-patient setting
12.7.5 Management of Cytokine Release Syndrome	Participants with increased cardiovascular risk factors (per Section 9.3.6) might need earlier intervention with tocilizumab and/or steroids at the onset of CRS. If CRS $\geqslant$ Grade 2 is suspected, an ECHO/MUGA is required at onset. If CRS $\geqslant$ Grade 2 additional monitoring should include: • Continuous cardiac telemetry monitoring • ECHO/MUGA as clinically indicated • Daily troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) or BNP tests.	Section was revised to specify management of patient with an increased burden of cardiovascular risk factors.

Section # and Name	Description of Change	Brief Rationale
Substudy 1		
2 Schedule of Activities Table 2	Footnote 11 was added for additional monitoring requirement if suspected CRS Grade $\geqslant$2. Footnote 14 was amended to indicate that participants with an increased burden of cardiovascular risk factors (as per Section 9.3.6) will undergo evaluation by a cardiologist prior to lymphodepletion. Footnote 29 was added to ensure collection of a Transgene Copies (Persistence for Safety) in case of any SAE that occurs after T-cell infusion. Footnote 30 was updated to align with recent revisions made in related protocols A cyclophosphamide infusion timepoint was added on Day -6. Removal of requirement for Creatinine Clearance (CrCl) assessment originally scheduled at months 18 and 30. Serum creatinine test maintained at these timepoints as part of chemistry panel and can still provide an estimaetion of CrCl.	These revisions were made to align with additional safety cardiac monitoring requirements These revisions were made to maintain consistency among studies for this investigative therapy. The revision was made to implement the optimized cyclophosphamide regimen schedule over 3 days. Optimization of the schedule of assessments and reduction of burden to participants.
2 Schedule of Activities Table 3	Removal of Microbiome Stool sample row and footnote 10.	Removal of Microbiome Stool sample collection as assay is deprioritized.
3.2.1 Risk assessment	Added potential risk of cardiac arrest. Added identified risk of haemorrhage secondary to thrombocytopenia	Updated risk assessment table to align with Dear Investigator Letter and recent safety events
5.1 Overall Design	The note under Part 1: Screening was updated to align with text in Section 6.3 of the Core Protocol.	This revision was made for consistency across sections in the core and substudy sections of the protocol.
5.5.1 Justification of Lymphodepleting Regimen	Text was updated to revise the cyclophosphamide dose from 1800 mg/m^2 x 2 days to 900 mg/m^2 x 3 days. In addition, justification for this change was added.	The lymphodepleting chemotherapy regimen was updated in order to mitigate risk of acute and prolonged toxicities while not compromising efficacy.
5.5.2 Justification of lete-cel (GSK3377794) Dose	The dose range maximum was expanded from 8×10^9 transduced T cells to 15×10^9 transduced T cells for participants treated under protocol amendments 6 and beyond.	The dose range maximum was updated in order to maximize the use of cells in participants whose manufacture yields >8×10^9 transduced T cells.

Section # and Name	Description of Change	Brief Rationale
6.1.1 Target Expression Screening Inclusion #3	Inclusion was simplified at this stage by postponing requirement for evidence of disease-specifc translocation to Leukapheresis Eligibility Screening (Inclusion #9)	This revision was made to allow target expression screening to proceed while evidence of disease-specifc translocation is being obtained.
6.1.2 Leukaperesis Eligibility Screening Inclusion #9 (newly added)	Requirement for evidence of disease-specifc translocation is being added at Leukapheresis Eligibility Screening stage with clarification on the requirement of gene involvements and update to the methods typically used for translocation identification.	This revision was made for optimization of the inclusion language on disease-specifc translocations.
Inclusion #11	The note under inclusion #11 was updated to align with text in Section 6.3 of the Core Protocol.	This revision was made for consistency across sections in the core and substudy sections of the protocol.
Inclusion #15	The alternative threshold for hemoglobin under Table 5 was corrected from 5.6 to 5.0 mmol/L to match with the original threshold of 8 g/dL.	This correction was made to align the 2 thresholds for haemoglobin expressed in different units..
6.2.2 Leukaperesis Eligibility Screening Table 6 Washout periods for Substudy 1	Washout period for radiotherapy only applies prior to lymphodepletion.	This revison was made to clarify that the radiotherapy washout period requirement only applies prior to lymphodepletion and not prior to leukapheresis.
Exclusion #10	Ongoing or active infection (including, but not limited to systemic fungal infection) are excluded	This revison was made to clarify that any systemic fungal infection is excluded
6.2.3 Treatment Eligibility Screening Exclusion #22	The text was amended to exclude participants with all measurable lesions irradiated within 3 months prior to lymphodepletion, exhausting the possibility of picking a target lesion for RECIST v1.1 assessment..	This revison was made to allow irradiation to measurable lesions as long as there are measurable lesions spared to be used as target lesions .
7.1.3 Lymphodepleting Chemotherapy	Text was added that refers to Table 7 for dose adjustment of participants ≥60 years of age. In addition, the cyclophosphamide doses were revised in Table 7. In the Mesna subsection, the cyclophosphamide dose was updated.	The revisions were made to clarify the dose adjustments and provide consistency with Section 5.5.1.

Section # and Name	Description of Change	Brief Rationale
7.5.1 Prohibited Concomitant Medications and Treatments	Text was added to specifiy that the listed prohibited therapies during the Interventional Phase of the study are those that are anti-cancer therapies.	Revisions were made to clarify the language on prohibited Concomitant Medications and Treatments.
10.3.1 Efficacy Analyses	In subsection “Final Efficacy Analysis” the ORR reporting was redefined by removing the phrase: (participants) “who have had at least two post-baseline disease assessments or have died or progressed or have withdrawn from the study.”	This revision was made to align with the Statistical Analysis Plan.
10.3.2 Safety Analysis	Text was clarified that listings may be provided in lieu of summaries in case of low-event counts. “Left ventricular function (ECHO and MUGA)” were removed from the clinical laboratory evaluations.	These revisions were made to align with the Statistical Analysis Plan.

Section # and Name	Description of Change	Brief Rationale
Substudy 2		
2 Schedule of Activities Table 2	Footnote 11 was added for additional monitoring requirement if suspected CRS Grade ⩾2. Footnote 14 was amended to indicate that participants with an increased burden of cardiovascular risk factors (as per Section 9.3.6) will undergo evaluation by a cardiologist prior to lymphodepletion. Footnote 29 was added to ensure collection of a Transgene Copies (Persistence for Safety) in case of any SAE that occurs after T-cell infusion. Footnote 30 was updated to align with recent revisions made in related protocols. Footnote 33 was updated to add instructions for completing the Healthcare Utilization Worksheet. A cyclophosphamide infusion timepoint was added on Day -6. Removal of requirement for Creatinine Clearance (CrCl) assessment originally scheduled at months 18 and 30. Serum creatinine test maintained at these timepoints as part of chemistry panel and can still provide an estimaetion of CrCl.	These revisions were made to align with additional safety cardiac monitoring requirements These revisions were made to maintain consistency among studies for this investigative therapy. The revision was made to improve collection of Healthcare Utilization. The revision was made to implement the optimized cyclophosphamide regimen schedule over 3 days. Optimization of the schedule of assessments and reduction of burden to participants.
2 Schedule of Activities Table 3	Removal of Microbiome Stool sample row and footnote 10.	Removal of Microbiome Stool sample collection as the assay was deprioritized.
3.2.1 Risk assessment	Added potential risk of cardiac arrest. Added identified risk of haemorrhage secondary to thrombocytopenia	Updated risk assessment table to align with Dear Investigator Letter and recent safety events
4 Objectives and Endpoints	The endpoint for the treatment-related healthcare resource utilization objective was revised (i.e., “treatment-related” changed to “oncology-related” and an example added).	To clarify the healthcare objective.
5.1 Overall Design 5.2 Number of Participants 5.4 Scientific Rationale for Substudy Design	The planned participant numbers were changed from 55 to 72. The intended number of participants who ultimately receive therapy and completed a minimum of 6-month follow-up or have died or have withdrawn early following lete-cel treatment was changed from 45 to 60.	Substudy 2 sample size increase to ensure greater statistical power and to align with the Core Protocol.

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	The note under Part 1: Screening was updated to align with changes made to the text in Section 6.3 of the Core Protocol.	This revision was made for consistency across sections in the core and substudy sections of the protocol.
5.5.1 Justification of Lymphodepleting Regimen	Text was updated to revise the cyclophosphamide dose from 1800 mg/m^2 x 2 days to 900 mg/m^2 x 3 days. In addition, justification for this change was added.	The lymphodepleting chemotherapy regimen was updated in order to further optimize and reduce potential for acutre and prolonged toxicities while also minimizing the impact on efficacy.
5.5.2 Justification of lete-cel (GSK3377794) dose	The upper end of the target dose range was increased from 8×10^9 transduced T cells to 15×10^9 transduced T cells for participants treated as of protocol amendment 6	Revisions were made in order to maximize the delivery of cells for participants whose manufacture yields >8×10^9 transduced cells.
6.1.1 Target Expression Screening Inclusion #3 Inclusion #5 was moved to Section 6.1.2 (Leukapheresis Eligibility Screening) to become Inclusion #9	 Inclusion was simplified at this stage by postponing requirement for evidence of disease-specifc translocation to Leukapheresis Eligibility Screening (Inclusion #8) Requirement for participant to be either currently treated with or have completed at least one standard of care treatment including anthracycline-containing regimens was moved to Leukapheresis Eligibility screening. A note was added to indicate that participants with advanced (metastatic or unresectable) disease can also still undergo leukapheresis prior to initiating first line or standard therapy. Removal of “within 12 weeks” restriction on eligibility requirement of progression post completion of anthracycline-based therapy in neoadjuvant/adjuvant setting.	 This revision was made to allow target expression screening to proceed while evidence of disease-specifc translocation is being obtained. Revisions were made to clarify the timing of eligibility in regards to prior line of standard of care treatment. Harmonization of language with Inclusion #17 to ensure that participants who have received anthracycline-based therapy as neoadjuvant, would still be eligible even if they were not able to receive anthracycline as 1L metastatic treatment.
6.1.2 Leukapheresis Eligibility Screening Inclusion #8 (newly added)	 Requirement for evidence of disease-specifc translocation is being added at Leukapheresis Eligibility Screening stage with clarification on the requirement of gene involvements and update to the methods typically used for translocation identification.	 This revision was made for optimization of the inclusion language on disease-specifc translocations.

Section # and Name	Description of Change	Brief Rationale
Inclusion #9 (moved from prior Inclusion #5)	Requirement for participant to be either currently treated with or have completed at least one standard of care treatment including anthracycline-containing regimens was moved to Leukapheresis Eligibility screening.	Revisions were made to clarify the timing of eligibility in regards to prior line of standard of care treatment.
Inclusion #10	The note under inclusion #10 was updated to align with text in Section 6.3 of the Core Protocol.	This revision was made for consistency across sections in the core and substudy sections of the protocol.
Inclusion #14	The alternative threshold for hemoglobin under Table 5 was corrected from 5.6 to 5.0 mmol/L to match with the original threshold of 8 g/dL.	This correction was made to align the 2 thresholds for haemoglobin expressed in different units.
6.1.3 Treatment Eligibility Screening Inclusion #20	The requirement that radiographic evidence of disease progression adhere to “RECIST v1.1 from prior line of therapy” was removed	This revision was made to allow for greater flexibility in patient treatment.
6.2.2 Leukaperesis Eligibility Screening		
Table 6 Washout periods for Substudy 2	Washout period for radiotherapy only applies prior to lymphodepletion.	This revison was made to clarify that the radiotherapy washout period requirement only applies prior to lymphodepletion and not prior to leukapheresis.
Exclusion #9	Ongoing or active infection (including, but not limited to systemic fungal infection) are excluded	This revison was made to clarify that any systemic fungal infection is excluded
6.2.3 Treatment Eligibility Screening Exclusion #21	The text was amended to exclude participants with all measurable lesions irradiated within 3 months prior to lymphodepletion, exhausting the possibility of picking a target lesion for RECIST v1.1 assessment..	This revison was made to allow irradiation to measurable lesions as long as there are measurable lesions spared to be used as target lesions .
7.1.3 Lymphodepleting Chemotherapy	Text was added that refers to Table 6 for dose adjustment of participants ≥60 years of age. In the Mesna subsection, the cyclophosphamide dose was updated.	Revisons were made to clarify the dose adjustments and revision of doses for consistency with Section 5.5.1.
7.5.1 Prohibited Concomitant Medications and Treatments	Text was added to specifiy that the listed prohibited therapies during the Interventional Phase of the study are those that are anti-cancer therapies.	Clarification of language on prohibited Concomitant Medications and Treatments.

Section # and Name	Description of Change	Brief Rationale
9.3 Healthcare Resource Utilization	The title was changed from "Medical and Health Economics Resource Utilization" to "Healthcare Resource Utilization." The text was replaced to clarify the healthcare resource data collection process and to remove patient paper form.	The text was replaced to clarify the data collection process and the information collected.
10.1 Statistical Hypotheses	A hierarchical testing strategy is being implemented: • Interim Analysis 1: After approximately 20 patients infused with intended commercial drug product supply and followed for approximately 3 months. No early claim for efficacy nor alpha adjustment are planned for this analysis. • Interim Analysis 2: After 45 patients infused with intended commercial drug product supply and followed for approximately 6 months, efficacy will be evaluated for the overall population (SS+MRCLS). • Primary Efficacy Analysis: After 60 patients infused with intended commercial drug product supply and followed for approximately 6 months, efficacy will be evaluated for the overall population (SS+MRCLS). Observing an ORR of 16 of 60 responders would provide a successful outcome for the study. • Primary Efficacy Analysis (SS sub-population): After 60 patients (SS+MRCLS) infused with intended commercial drug product supply and followed for approximately 6 months, the SS sub-population will be evaluated.	This section was updated to reflect the increase in sample size and clarify the hierarchical testing strategy
10.2 Sample Size Justification	The sample size was changed from 45 to 60. Thus, the ORR needed to claim success at the time of primary analysis was changed from "(12/45)" to "(16/60)." A hierarchical testing strategy for an interim analysis and primary efficacy analysis was added.	The sample size was updated to align with revisions in previous sections.
10.3 Populations for analyses	Participants who received drug product supply that was released as a "non conforming batch" will not be included in mITT, mITTc, PEAP and PEAPi populations	The definition of the populations for analyses was updated to specify how participants treated under a "non-conforming batch" release will be analysed.
10.5.2 Safety Analyses	Text was clarified that listings may be provided in lieu of summaries in case of low-event counts.	The text was revised to clarify the processing of listings.

Section # and Name	Description of Change	Brief Rationale
10.5.5 Interim Analyses	A second interim analysis was added, and changes were made to clarify the plans for the first interim analysis.	The revisions were made to clarify the interim analysis plans for this study.
Throughout Core and rest of document		
	'GSK3377794' was replaced by 'lete-cel' throughout document only leaving reference to GSK3377794 when relevant.	To generalize use of shortname 'lete-cel' deived from the GSK3377794's generic drugname "Letetresgene Autoleucel"
	Accrual numbers as well as lete-cel safety profile have been updated based on the most current Lete-cel Investigator's Brochure as of 27 January 2021.	

TABLE OF CONTENTS

PAGE

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1 SYNOPSIS

Protocol Title: Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered NY-ESO-1 specific (c259) T Cells, alone or in combination with other agents, in HLA-A2+ Participants with NY-ESO-1 and/or LAGE-1a Positive Solid Tumors (IGNYTE-ESO)

Short Title: Master Protocol to Assess the Safety and Antitumor Activity of Genetically Engineered T Cells in NY-ESO-1 and/or LAGE-1a Positive Solid Tumors

Rationale:

In this master protocol we will investigate T cells that have been genetically engineered to recognize NY-ESO-1 and LAGE-1a tumor antigens. Adoptive T-cell therapy (ACT) is a therapeutic approach that uses a cancer patient's own T lymphocytes obtained by leukapheresis, genetically engineered to express a tumor-targeting receptor, such as a T-cell receptor (TCR) or a chimeric antigen receptor (CAR), expanded *ex vivo* and re-infused into the participant, with the aim of generating and propagating an anti-tumor T-cell immune response.

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

In previous clinical trials using adoptively transferred T cells directed against NY-ESO-1/LAGE-1a, objective responses have been observed in 40 to $60^{\%}$ of treated participants who are HLA-A*02^{+}, bearing NY-ESO-1^{+} synovial sarcoma. Similar or higher response rates have been observed with this treatment in metastatic melanoma, and multiple myeloma post autologous stem cell transplant (ASCT). Letetresgene autoleucel (lete-cel, GSK3377794) is the first generation product consisting of autologous T cells expressing the affinity enhanced TCR (c259), and this is currently being investigated in ongoing GSK-sponsored pilot clinical trials in HLA-A*02^{+} participants with NY-ESO-1^{+} metastatic synovial sarcoma (208466 [ADP-04511]), advanced MRCLS (study 208469 [ADP-0011-007]), NSCLC (GSK study 208749 [ADP-0011-004] and GSK study 208471), and relapsed refractory multiple myeloma (study 208470 [ADP-0011-008]). A summary of the clinical data obtained to date with these TCR engineered NY-ESO-1/LAGE-1a targeting T cells is presented in the most current Lete-cel Investigator's Brochure.

This is a master protocol (208467) consisting of a core protocol with multiple independent substudies. The protocol will initially include a substudy to investigate letetresgene autoleucel (lete-cel, GSK3377794) treatment in previously untreated (1L) HLA-A*02^{+} participants with NY-ESO1^{+} advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma (Substudy 1). A separate substudy will investigate letetresgene autoleucel (lete-cel, GSK3377794) infusion as second line or higher (2L+) treatment in HLA-A*02^{+} participants with NY-ESO-1^{+} advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, who have progressed following treatment with anthracycline based chemotherapy for the purpose of registration (Substudy 2).

The protocol may be amended at a later time to add additional substudies to investigate other NY-ESO-1 or LAGE-1a positive tumor types and other NY-ESO-1 specific (c259) T cells (potentially in combination with other agents).

Objectives and Endpoints:

Objectives and endpoints are outlined in the substudies.

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 substudies.

Objectives	Endpoints
Primary	
To evaluate the efficacy of NY-ESO-1 specific (c259) T cells, alone or in combination with other anti-cancer agents, in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 and/or LAGE-1a positive solid tumors	Overall Response Rate (ORR) per RECIST v1.1[1]
Secondary - Efficacy	
To further evaluate the efficacy of NY-ESO-1 specific (c259) T cells alone or in combination with other anti-cancer agents in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 and/or LAGE-1a positive solid tumors	• Time to Response (TTR) • Duration of Response (DoR) • Disease Control Rate (DCR) • Progression Free Survival (PFS)
Secondary - Safety	
To evaluate the safety and tolerability of NY-ESO-1 specific (c259) T cells alone or in combination with other anti-cancer agents in HLA-A*02:01, HLA-A*02:05 and/or	• Frequency and severity of Adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in protocol) • Laboratory parameters • Replication Competent Lentivirus (RCL)

Objectives	Endpoints
HLA-A*02:06 participants with NY-ESO-1 and/or LAGE-1a positive solid tumors	• Instances of Insertional oncogenesis (IO)
Secondary - Pharmacokinetics	
To characterize *in vivo* cellular PK profile (levels, expansion, persistence) of NY-ESO-1 specific (c259) T cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit

AE/s = adverse events; AESI/s = adverse event/s of special interest; AUC(0-t) = area under the time curve from zero to time t; Cmax = maximum concentration; DCR = disease control rate; DoR = duration of response; HLA = human leukocyte antigen; IO = insertional oncogenesis; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCL = replication competent lentivirus; RECIST = Response Evaluation Criteria In Solid Tumors; SAE/s = serious AE/s; Tmax = Time to Cmax; TTR = Time to Response

[1] Independent central review where applicable will be specified in the specific substudies.

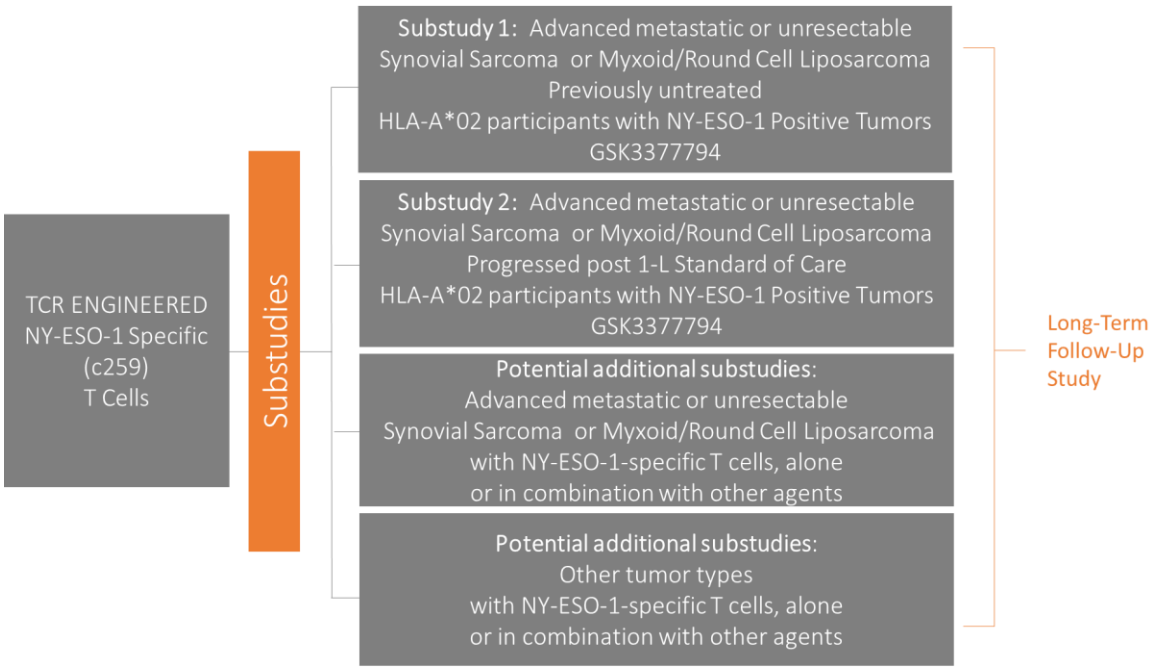
Overall Design:

This is a master protocol to investigate the safety and antitumor activity of TCR engineered NY-ESO-1 specific (c259) T cells alone or in combination with other agents in HLA-A*02^{+} participants with NY-ESO-1 and/or LAGE-1a positive solid tumors.

The protocol will initially evaluate a first generation of NY-ESO-1 specific TCR (c259) engineered T cells, letetresgene autoleucel (lete-cel, GSK3377794), in HLA-A*02^{+} participants with NY-ESO-1^{+} advanced metastatic or unresectable synovial sarcoma.

The protocol may be amended later to investigate the activity of TCR engineered NY-ESO-1 specific (c259) T cells in other NY-ESO-1^{+} or LAGE-1a^{+} tumor types or in combination with other agents (see the Study Design schematic below). Details of treatment will be provided in the specific substudies.

Unless otherwise specified in a substudy, participants will receive a single dose of NY-ESO-1 specific (c259) T cells after completing lymphodepleting chemotherapy.



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

Number of Participants:

As this is a master protocol consisting of multiple substudies, the overall sample size is not fixed. The initial number of participants is expected to be approximately 97 in Substudies 1 and 2 combined. Substudy 1 will enrol 10 participants with previously untreated advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, that is either newly diagnosed or relapsed after surgery and radiotherapy and/or adjuvant therapy. Substudy 2 will enrol approximately 87 participants previously treated with anthracycline-based regimen for advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, including :

- Approximately 15 participants expected to receive the clinical drug product supply;
- Approximately 72 participants will be enrolled to ensure that at least 60 participants will receive letetresgene autoleucel (letecel, GSK3377794) using commercial vector supply and manufacturing process. An additional 20% enrollment is factored in between leukapheresis and dosing to account for: early withdrawal, manufacturing issues, and extended waiting-time for progression.

Any additional substudies will be added via protocol amendments with specification of number of participants for each substudy.

Methodology and Study Duration:

Participants identified by the Investigator as possible candidates for a substudy must have completed preliminary target expression screening for HLA-typing and NY-ESO-1 or

LAGE-1a antigen expression (Note: target expression screening may also be performed under a separate GSK-sponsored screening protocol or under another GSK-sponsored NY-ESO-1 and/or LAGE-1a targeting T-cell protocol or substudy). Participants with the HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 alleles and whose tumor expresses the NY-ESO-1 or LAGE-1a antigen (as specified in each substudy) by validated testing at a designated central laboratory are eligible to undergo further screening under this protocol.

Following screening, participants who meet substudy entry criteria will be eligible to the study. Eligible participants will undergo leukapheresis to collect autologous T cells to manufacture TCR engineered NY-ESO-1 specific (c259) T cells; the Investigational Product. The successful initiation of leukapheresis procedure constitutes enrollment in the study.

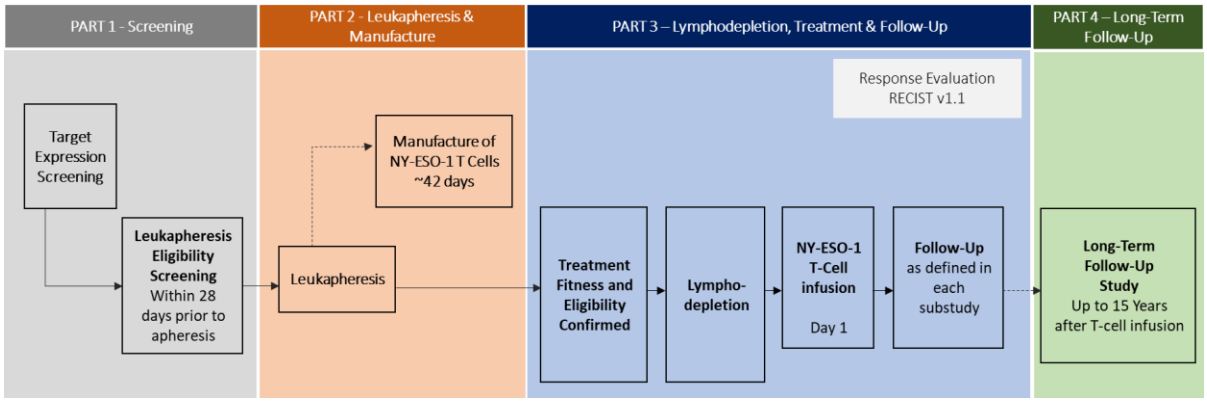
Once the TCR engineered NY-ESO-1 specific autologous (c259) T cells have been successfully manufactured, released, and are available for infusion at the site, and once participants' fitness for lymphodepletion has been assessed and additional eligibility criteria for treatment are met, participants will then receive lymphodepleting chemotherapy as specified within each substudy. Lymphodepleting chemotherapy may be given as outpatient treatment per institutional guidelines.

The investigational product, TCR engineered NY-ESO-1 specific (c259) T cells , will be administered as a single intravenous (IV) infusion on Day 1, unless otherwise indicated in a specific substudy. Participants will be hospitalized on the day of T-cell infusion (Day 1) and may be in the hospital for follow-up care until Day 3 as clinically indicated. Through Day 14, participants must be closely monitored by the Investigator. Additional close monitoring or hospitalization may be warranted based upon clinical need and is at Investigator's discretion. Participants will receive growth factor support with Granulocyte-Colony Stimulating Factor (G-CSF) from ~24 hours following lymphodepleting chemotherapy (i.e. on Day -3) until neutrophil count recovery in accordance with ASCO guidelines [Smith, 2015] or institutional practice.

After NY-ESO-1 specific (c259) T-cell infusion, participants are followed in the interventional portion of a given substudy until confirmed disease progression at which time the participants enter the follow up phase. All participants will be followed for the period defined in each specific substudy, and subsequently entered into a separate long-term follow-up (LTFU) protocol (GSK study 208750) for up to 15 years after T-cell infusion for gene therapy related adverse events per health authority guidance.

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.

Participant Journey Schema



Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) consisting of external experts has been established for ongoing review of safety events and efficacy to enable benefit/risk determination for all substudies of this master protocol, independent of the study team. Additional details is provided in an IDMC Charter.

Key recommendations of the IDMC will be documented and reported to regulatory agencies if requested, all participating Principle Investigators (PIs) and if required, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) as appropriate with impactful decisions communicated as priority.

2 SCHEDULE OF ACTIVITIES (SOA)

Schedule of activities will be documented in each substudy.

3 INTRODUCTION

This is a master protocol investigating the safety and antitumor activity of genetically engineered autologous NY-ESO-1 specific (c259) T-cells alone or in combination with other agents in HLA-A*02+ participants with NY-ESO-1 and/or LAGE-1a positive solid tumors.

This master protocol consists of a core protocol with multiple independent substudies. The protocol will initially include a substudy to investigate letetresgene autoleucel (lete-cel, GSK3377794) treatment in previously untreated (1L) HLA-A*02^{+} participants with NY-ESO-1^{+} advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma (Substudy 1). A separate substudy will investigate letetresgene autoleucel (lete-cel, GSK3377794) infusion as second line or higher (2L+) treatment in HLA-A*02^{+} participants with NY-ESO-1^{+} advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, who have progressed following treatment with anthracycline based chemotherapy for the purpose of registration (Substudy 2).

The protocol may be amended at a later time to add additional substudies to investigate other NY-ESO-1 or LAGE-1a positive tumor types and other NY-ESO-1 specific (c259) T cells (potentially in combination with other agents).

3.1 Study Rationale

In this protocol we will investigate T cells that have been genetically engineered to recognize NY-ESO-1 and LAGE-1a tumor antigens. Adoptive T-cell therapy (ACT) is a therapeutic approach that uses a cancer patient's own T lymphocytes obtained by leukapheresis, genetically engineered to express a tumor-targeting receptor, such as a T-cell receptor (TCR) or a chimeric antigen receptor, expanded *ex vivo* and re-infused into the participant, with the aim of generating and propagating an anti-tumor T-cell immune response.

NY-ESO-1 and LAGE-1a are members of the cancer-testis family of tumor antigens (CTAs). NY-ESO-1 is a cytoplasmic protein that is detectable in multiple cancer types including non-small cell lung cancer (NSCLC), bladder cancer, malignant melanoma, liver cancer, synovial sarcoma, myxoid/round cell liposarcoma (MRCLS), and many others. Specific peptide epitopes of the NY-ESO-1 or LAGE-1a protein are processed and presented on the surface of the tumor cell in complex with an HLA molecule, which can be recognized by T cells. An HLA-A2 binding peptide ($SLLMWITQC_{aa\ 157\text{-}165}$) that is common to both NY-ESO-1 and LAGE-1a antigens has been identified that can be recognized by NY-ESO-1 reactive T-cells. The T cells for therapy have been genetically engineered to express an affinity enhanced T-cell receptor toward the SLLMWITQC peptide bound to HLA-A*02. The retained optimized TCR clone was called $NY\text{-}ESO\text{-}1^{c259}$ or c259. The T-cell product consists of autologous T cells transduced with a self-inactivating lentiviral vector encoding the affinity enhanced NY-ESO-1 specific TCR (c259).

In previous clinical trials using adoptively transferred T cells directed against NY-ESO-1/LAGE-1a, objective responses have been observed in 40 to $60^{\%}$ of treated participants who are $HLA\text{-}A*02^{+}$ bearing $NY\text{-}ESO\text{-}1^{+}$ synovial sarcoma [Robbins, 2011; Robbins, 2015; D'Angelo, 2018b]. 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, 2015].

3.2 Background

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. 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 enhanced safety, anti-tumor activity of TCR engineered cells, as well as enhanced persistence of the infused TCR engineered T cells compared to CAR-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].

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]. The incorporation of lymphodepletion prior to ACT may enhance immune reconstitution by the transferred cells and increase tumor-specific responses. Immune reconstitution is enhanced through homeostatic mechanisms that facilitate expansion of T lymphocytes [Baccala, 2005], 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 the induction of inflammatory cytokines and induction of tumor apoptosis with resulting cross presentation of tumor antigens to T cells.

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 synovial sarcoma. The estimated overall three and five-year survival rates for patients with synovial sarcoma were 38% and 14%, respectively [Robbins, 2015]. No toxicity attributed to the infused cells was reported in these studies.

This protocol 208467 initially includes letetresgene autoleucel (lete-cel, GSK3377794), for which background information is provided below. Should other NY-ESO-1 specific (c259) T cells or combination agents be added in future, any applicable background information will be added via amendment.

3.3 GSK3377794 (letetresgene autoleucel, lete-cel)

Lete-cel is the first generation product consisting of autologous T cells transduced with lentiviral vectors to express the affinity enhanced TCR (c259) and is currently being investigated in ongoing GSK sponsored pilot clinical trials in HLA-A*02^{+} participants with NY-ESO-1 and/or LAGE-1a positive metastatic synovial sarcoma (SS) (208466 [ADP-04511]), advanced myxoid/ round cell liposarcoma (MRCLS) (study 208469

[ADP-0011-007]), non-small cell lung cancer (NSCLC) (GSK study 208749 [ADP-0011-004] and GSK study 208471), and relapsed refractory multiple myeloma (MM) (study 208470 [ADP-0011-008]).

The most recent summary of the ongoing studies and clinical data obtained to date with these TCR engineered NY-ESO-1/LAGE-1a targeting T cells is presented in the most current Lete-cel Investigator's Brochure.

Lete-cel in combination with other anti-cancer agents such as PD-1/PD-L1 blocking agents like pembrolizumab is also being evaluated in MM (208470/ADP-0011-008) and in NSCLC (208471). In addition, an observational long-term follow-up study (Study 208750) is being conducted in participants exposed to lete-cel in previous clinical trials as required for gene therapy products [EMA, 2009; FDA, 2020a; FDA, 2020b].

As of 27 January 2021, 125 participants have received lete-cel across tumour types including SS, MM, MRCLS and NSCLC, investigated in our ongoing clinical programmes. The efficacy and safety of lete-cel is described in the most current version of Lete-cel Investigator's Brochure and summarized in the benefit/risk assessment in the relevant specific substudies.

4 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are outlined in the substudies.

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 substudies.

Objectives	Endpoints
Primary	
To evaluate the efficacy of NY-ESO-1 specific (c259) T cells, alone or in combination with other anti-cancer agents, in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 and/or LAGE-1a positive solid tumors	Overall Response Rate (ORR) per RECIST v1.1[1]
Secondary - Efficacy	
To further evaluate the efficacy of NY-ESO-1 specific (c259) T cells alone or in combination with other anti-cancer agents in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 and/or LAGE-1a positive solid tumors	• Time to Response (TTR) • Duration of Response (DoR) • Disease Control Rate (DCR) • Progression Free Survival (PFS)
Secondary - Safety	
To evaluate the safety and tolerability of NY-ESO-1 specific (c259) T cells alone or in combination with other anti-cancer agents in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 and/or LAGE-1a positive solid tumors	• Frequency and severity of Adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in protocol) • Laboratory parameters • Replication Competent Lentivirus (RCL) • Instances of Insertional oncogenesis (IO)
Secondary - Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 specific (c259) T cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit

AE/s = adverse event/s; AESI/s = adverse event/s of special interest; AUC(0-t) = area under the time curve from zero to time t; Cmax = maximum concentration; DCR = disease control rate; DoR = duration of response; HLA = human leukocyte antigen; IO = insertional oncogenesis; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCL = replication competent lentivirus; RECIST = Response Evaluation Criteria In Solid Tumors; SAE/s = serious AE/s; Tmax = Time to Cmax; TTR = Time to Response

[1] Independent central review where applicable will be specified in the specific substudies.

5 STUDY DESIGN

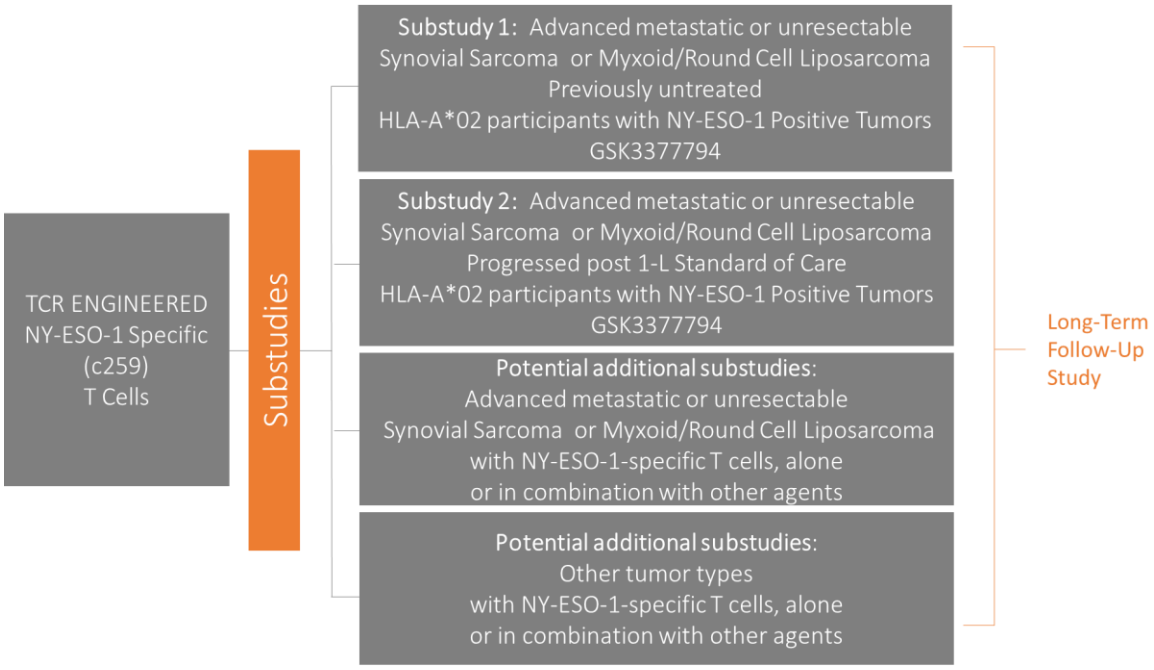
5.1 Overall Design

This is a master protocol investigating the safety and antitumor activity of TCR engineered NY-ESO-1 specific (c259) T-cells alone or in combination with other agents in HLA-A*02 $^{+}$ participants with NY-ESO-1 and/or LAGE-1a positive advanced solid tumors.

The protocol will initially evaluate a first generation of NY-ESO-1 specific TCR (c259) engineered T-cells, letetresgene autoleucel (lete-cel, GSK3377794), in HLA-A*02^{+} participants with NY-ESO-1^{+} advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.

The protocol may be amended later to investigate the activity of other TCR engineered NY-ESO-1 specific (c259) T-cells in other NY-ESO-1^{+} or LAGE-1a $^{+}$ tumor types and/or in combination with other agents (see Figure 1 Study Design schematic below). Details of treatment are provided in the substudies.

Figure 1 Study Design



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

Participant Journey

Unless otherwise specified in a given substudy, participants will undergo stepwise enrollment followed by treatment according to defined phases within each substudy (See Figure 2 Participant Journey Schema below) which will include the following:

Part 1: Screening

1) Target expression screening for the presence of HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positivity and tumor expression of NY ESO-1 and/or LAGE-1a,

   (Note: If a participant was previously tested for HLA and NY-ESO-1/LAGE-1a expression under a different GSK-sponsored protocol, testing of HLA and/or NY-ESO-1 for 208467 may not be required dependent on the test platform(s) used and whether they meet the 208467 protocol requirements [see Section 6.3])

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 for safety and final Treatment eligibility screening,

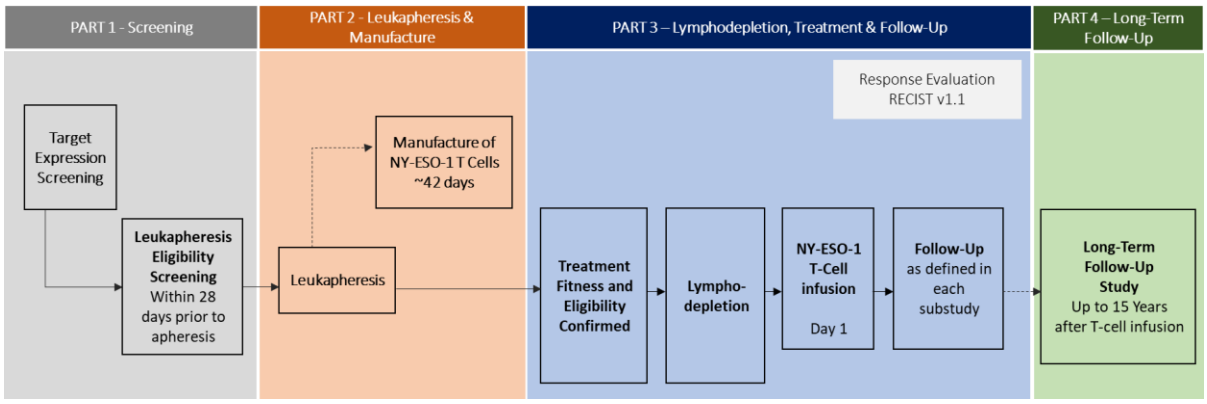
5) Interventional phase including Lymphodepletion from Days-7 to -4, TCR engineered T-cell infusion on Day 1 and follow-up as defined in each specific substudy,

   (Note: TCR engineered T-cell 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.

Figure 2 Participant Journey Schema



Part 1: Screening

Screening will consist of two phases: target expression screening and leukapheresis eligibility screening.

Target expression screening (i.e. HLA type and tumor NY-ESO-1/LAGE-1a antigen expression) may start at any time after diagnosis of high-risk locally advanced disease

(i.e. deeply seated, high grade, positive margins, large [≥5 cm], or locally recurrent) for Substudy 1, or advanced (metastatic or unresectable) disease for Substudy 2, subject to any substudy specific requirements. Disease recurrence or progression may be present but is not mandatory for screening.

For target expression 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. In the future, if a tumor type is known to express NY-ESO-1 and/or LAGE-1a in a high percentage of cases, testing for the antigen expression may be omitted.

Once participants are deemed positive for HLA and tumor antigen expression, 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

Leukapheresis can be initiated following confirmation of eligibility for leukapheresis, which includes a series of lab assessments required to be completed within 7 days from the day of leukapheresis.

The initiation of leukapheresis procedure constitutes enrollment in the study.

Disease progression may be present but is not mandatory for leukapheresis. In addition leukapheresis may occur before, during or upon completion of a prior line of therapy.

Upon development of progressive disease in metastatic cancer patients, the disease may have a rapid course, and any treatment delay can limit the treatment effect. Manufacture of autologous T cells (lete-cel, GSK3377794) requires an average of 35-42 days.

Because of this, the potential for early leukapheresis is justified based on the following:

- Early Leukapheresis permits the manufacture of T cells prior to progression of disease from prior therapy. This then permits timely treatment of the patient, thereby improving chances of a treatment effect.
- Leukapheresis product collected prior to intense chemotherapy treatment may contain T cells that have higher proliferative potential thereby providing higher yield of a fitter T-cell product.
- Manufacturing failures can be communicated ahead of time, thereby, minimizing delays for further treatment if product is not available in time for the patient.

The cryopreserved T-cell product from leukapheresis is stable for 2 years. The cryopreserved drug product (NY-ESO-1 specific (c259) T cells) is also stable for 2 years.

It is expected that early leukapheresis can be safely performed in a participant receiving either chemotherapy and / or targeted agents, as long as the protocol specified leukapheresis eligibility requirements are satisfied. In general, leukapheresis is well tolerated. Side effects during the procedure may include numbness and/or tingling in the extremities or muscle twitching due to the anticoagulant used in the machine. Low blood pressure with light-headedness, chest discomfort, and/or shortness of breath may occur at the beginning of the procedure. Uncommon events include fainting, pain, nausea, vomiting, blood clotting difficulties, fatigue, and/or bruising at the needle injection sites. Extremely rare events may include air embolism, blood loss from accidental leakage from tubing, infection, difficulty breathing, transient arrhythmias, shock, or heart failure. Both the Investigators and potentially eligible participants will be fully informed and aware of these potential risks. Also, sites are chosen based on expertise for managing any potential risks associated with NY-ESO-1 specific (c259) T cells and/or procedural risks. Adverse events will be monitored as described in Section 9.4.1.

Following leukapheresis, T-cell manufacture will be undertaken.

Unless otherwise specified in a specific substudy, bridging or standard of care intermediate anti-cancer therapies [e.g. chemotherapy, local therapy (e.g. radiotherapy, cryoablation, surgical resection, etc.)] 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 specific substudies)

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

A baseline scan is performed prior to lymphodepletion to confirm the presence of measurable disease and then the participant will receive T-cell infusion and be followed as per RECIST v1.1 for efficacy analysis and per iRECIST for treatment decisions.

Participants who have failed screening or withdrawn before T-cell infusion, may rescreen in the same substudy or consider entering screening for another substudy (see Section 6.2 for further details).

Part 3: Lymphodepletion/Treatment

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 within 10 days prior to initiating lymphodepleting chemotherapy.

2. Baseline radiological tumor assessment is obtained within 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 prior to initiating lymphodepletion is required. This biopsy will be used as baseline for biomarker analyses. If it is not feasible to obtain a fresh biopsy, 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 bridging or standard of care intermediate anti-cancer therapy, the screening biopsy will be used for baseline.

Following lymphodepletion, after ~24 hours of completing lymphodepleting chemotherapy (i.e., on Day -3), participants must receive Granulocyte-Colony Stimulating Factor (G-CSF) support in accordance with ASCO guidelines [Smith, 2015] or institutional practice. The formulation of G-CSF to be used can be decided by the Investigator based on the institutional practice.

Participants will be hospitalized on the day of T-cell infusion (Day 1) and may be in the hospital for follow-up care until Day 3 as clinically indicated. Through Day 14, participants must be closely monitored by the Investigator. Additional close monitoring or hospitalization may be warranted based upon clinical need and is at Investigator's discretion (please refer to Section 9.3 for safety assessments and monitoring; Section 9.4 for reporting of adverse events; and Section 12.7 for supportive care guidance on T-cell infusion, CRS and other potential risks).

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

Participants who are not eligible for study intervention by the time NY-ESO-1 specific (c259) 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, 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)

At the end of the study for each participant (as defined in Section 5.3.1), and no sooner than 90 days post T-cell infusion (in order to capture minimal safety information),

participant will be entered into a separate LTFU protocol (GSK study 208750) and will be monitored for up to 15 years post T-cell infusion.

5.2 Number of Participants

As this is a master protocol consisting of multiple substudies, the overall sample size is not fixed. The initial number of participants is expected to be approximately 97 in Substudies 1 and 2 combined. Substudy 1 will enroll 10 participants with previously untreated advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, that is either newly diagnosed or relapsed after surgery and radiotherapy and /or adjuvant therapy. Substudy 2 will enroll approximately 87 participants previously treated with anthracycline-based regimen for advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, including :

- Approximately 15 participants expected to receive the clinical drug product supply;
- Approximately 72 participants will be enrolled to ensure that at least 60 participants will receive letetresgene autoleucel (lete-cel, GSK3377794) using commercial vector supply and manufacturing process. An additional 20% enrollment is factored in between leukapheresis and dosing to account for: early withdrawal, manufacturing issues, and extended waiting-time for progression.

Any additional substudies will be added via protocol amendments with specification of number of participants for each substudy.

Refer to the substudies for additional details on sample size determinations.

5.3 End of Master Protocol Definition

5.3.1 End of Study for Individual Participants

Refer to the substudies (including Substudy 1-Section 5.3 and Substudy 2-Section 5.3) for end of substudy definitions for Individual Participants.

5.3.2 End of Master Protocol

This Master Protocol will end as of the last visit of the last participant in the last sub-study, or when all participants have met their respective substudy end criteria including those who have died, withdrawn consent or are lost to follow-up.

Subject to specific criteria outlined in each substudy, in general any participant who has not reached progressive disease by end of substudy or is still being followed in long-term follow-up phase by end of substudy will be transferred to a separate long-term follow up protocol (GSK study 208750) for observation of delayed AEs and survival for a duration of up to 15 years post-T cell infusion in accordance with FDA [FDA, 2020a] and EMA guidance [EMA, 2009].

5.4 Scientific Rationale for Protocol Design

This is a master protocol design to evaluate TCR engineered NY-ESO-1 specific (c259) T cells alone or in combination with other agents in HLA-A*02^{+} participants with NY-ESO-1 and/or LAGE-1a Positive Solid Tumors via independent substudies.

The scientific rationale for each substudy is provided in each specific substudy.

5.4.1 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) consisting of external experts will be established for ongoing review of safety events and efficacy to enable benefit/risk determination, for all substudies of this master protocol, independent of the study team. Additional details will be provided in an IDMC Charter.

Key recommendations of the IDMC will be documented and reported to regulatory agencies if requested, all participating Principle Investigators (PIs) and if required, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) as appropriate with impactful decisions communicated as priority.

6 PROTOCOL POPULATION

Prospective approval of protocol deviations relating to enrollment criteria for the purpose of recruiting participants, also known as protocol waivers or exemptions, is not permitted.

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

Initially, the protocol will enroll participants with advanced (metastatic or unresectable) synovial sarcoma (SS) or myxoid/round cell liposarcoma (MRCLS) (Substudies1 and 2). Substudy 2 will be a registration substudy and will enroll participants with advanced metastatic or unresectable sarcomas or MRCLS who have progressed following anthracycline based chemotherapy.

Due to differences in entry criteria for the specific participant populations, all inclusion and exclusion criteria and lifestyle considerations are presented in the specific substudies.

Eligibility Screening will take place in the following 3 steps:

- Target Expression Screening: A set of criteria permitting participants' blood to be screened for HLA status and archival (most recent preferred) or fresh tumor biopsy samples to be screened for the expression of NY-ESO-1 and/or LAGE-1a.
- Leukapheresis Screening: Eligibility must be fulfilled prior to performing leukapheresis procedure.
- Lymphodepletion and Treatment Eligibility Screening: To be fulfilled prior to commencing lymphodepleting chemotherapy and administration of T cells.

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, and may also include disease characteristics, prior lines of anti cancer treatment, performance status and any serious adverse events (SAEs).

6.2 Rescreening

Individuals who do not meet the criteria for participation in a given substudy at any stage (screen failure or withdrawal) may be rescreened for any applicable substudy upon Sponsor agreement. Participants rescreened will be assigned a new participant number.

For each rescreened participant, the Sponsor will confirm the following on evaluation for an applicable substudy:

- Participant has previously tested positive for protocol-specified HLA typing by a validated test in a designated central laboratory;
- Participant's tumor has previously been pathologically reviewed by a Sponsor designated central laboratory with confirmed positive NY-ESO-1 and/or LAGE-1a antigen expression;
- Participant has previously completed Sponsor protocol-specified leukapheresis, and cryopreserved T cells or manufactured product are available and within shelf-life specifications.

6.3 Screening Under Other GSK Studies

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

Where a participant was previously tested for HLA and/or antigen expression under a different GSK-sponsored protocol, testing of HLA and/or antigen expression for 208467 may not be required dependent on the test platform(s) used and whether they meet the 208467 protocol requirements. If the Study 208467 testing requirements are not met, repeat test(s) may be required. The repeat test(s) may be possible without requiring 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. Additionally, if the NY-ESO-1 specific TCR engineered T cells are already manufactured for these participants, leukapheresis and/or re-manufacture process may not be necessary, in 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.

In general, however, study intervention will follow the steps outlined in Section 5.1 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 specific substudies.

8.1 Discontinuation of Study Intervention

As the T-cell intervention is administered as a single dose, 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 9.3 for safety assessments and monitoring; Section 9.4 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 min after thawing. When restarting infusion, new previously unthawed bag of cells needs to be used following Drug Product and Infusion Manual.

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.

8.2 Liver Chemistry Increased Monitoring Criteria

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

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

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.

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	• 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).

• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (pre-gene therapy) **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow-up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline (pre-gene therapy) • A specialist or hepatology consultation is recommended **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)	• Fractionate bilirubin, if total bilirubin ≥2xULN • If possible, obtain peripheral blood for persistence of genetically modified cells. • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **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 Temporary Discontinuation

NY-ESO-1 specific (c259) T-cell intervention is administered as a single dose via IV infusion. In the event of severe reactions associated with liver toxicities during infusion, the infusion may be interrupted. 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.
- At the time of study withdrawal, if possible, participant will be asked to consent to LTFU study.
- 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).
- Refer to the SoA in each substudy 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 are handled as part of Section 12.1.

8.5 Study Stopping and Pausing Rules

The study will pause enrollment and stop treatment for all participants if any of the following events occur pending submission to Regulatory Agencies and review by IDMC, IRBs/ECs, and the Sponsor:

- Any event of Guillain-Barré syndrome (GBS) as diagnosed by a neurologist according to diagnostic guidance for GBS [Fokke, 2014].
- A case of documented symptomatic progressive cerebral edema confirmed by an expert neurological examination and CT/MRI, that is not responding to treatment.
- A biologically functional positive Replication Competent Lentivirus (RCL) after 2 confirmed positive tests by PCR.
- Death directly attributed to lete-cel by the Investigator and IDMC.

Premature study termination may occur if:

- Sponsor, in consultation with IDMC, 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 underlying advanced malignancies in the initial and future substudies and these AEs 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, IDMC, 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, upon consultation with IDMC. Premature termination of individual substudies or the entire clinical study may occur because of a regulatory authority decision.

9 STUDY ASSESSMENTS AND PROCEDURES

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

Unless otherwise stated in a substudy 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, the substudy 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 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 Efficacy Assessments

See individual substudies for any additional assessments.

9.1.1 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.
- iRECIST will be used to aid in clinical decision making and for exploratory evaluations.

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

- Diagnostic-quality computed tomography (CT) scan with oral and/or IV iodinated 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, 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. The same imaging modality should be followed for each subsequent assessment.
- MRI of the extremities per site standard of care, if clinically indicated;

- Digital photographs of skin lesions including a ruler for estimating the size of the lesion.

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 NY-ESO-1-specific (c259) 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 was first met. For post-baseline assessments, a window is permitted to allow for flexible scheduling as defined in the SoA within each specific substudy.

Tumor images will be obtained 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.

9.1.2 Long-Term Follow-up

Upon the end of the applicable substudy for each participant, participant will be entered into a separate LTFU protocol (GSK study 208750) and will be monitored for up to 15 years post T-cell infusion.

9.2 Patient Reported Outcomes

Patient reported outcomes will be assessed as part of this protocol. Specifics regarding which measures will be employed are outlined in the substudies.

9.3 Safety Assessments

9.3.1 Safety Review Team

An internal Safety Review Team (SRT) is in place, consisting of a cross functional team of the appropriate disciplines required to ensure holistic evaluation of the safety profile of the NY-ESO-1 specific (c259) T-cell product under evaluation. The Safety review team conducts systematic, periodic and documented reviews of available safety data from all studies in the program and addresses the safety issues pertinent to the medicine.

9.3.2 Physical Examinations and Developmental 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 for each substudy.

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.

9.3.3 Additional Assessments for Pediatric Participants

For pediatric participants, height and weight will also be evaluated as a percentile vs national growth charts (based on sex and age) and vs genetic height target (expected height based on parental heights) and evaluation will be performed on whether growth is normal or abnormal.

For pediatric participants, puberty assessments will be undertaken once a year until puberty is completed. Puberty will be assessed by means of genital examination in the physical examination, completion of the Tanner scale, general questioning of the participant about their sexual activity, sexual potency (males) and menstrual cycles (females).

Developmental examinations will also be performed once a year.

9.3.4 Lansky, Karnofsky, or ECOG Performance Status

The performance status will be assessed per Table 1 below:

Table 1 Performance status scale

Participant age (years)	Performance status scale to be used (Section 12.9)
<16	Lansky
≥16 and < 18	Karnofsky
≥18	ECOG

using Lansky (for participants <16 years of age) or Karnofsky (for participants ≥16 and <18 years of age) or ECOG (for participants ≥18 years of age) scale (Section 12.9) at the time points specified in the SoA in each substudy. Participants who become 16 or 18 years of age during the study should switch to the age-appropriate index at that time.

9.3.5 Vital Signs

Blood pressure, pulse measurements (rate and oximetry), respiratory rate, and body temperature should be assessed per institutional standards. These will be assessed as per the SOA Tables in Section 2 of each substudy and recorded in the eCRF. The same methods should be used throughout the course of the substudy. 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, vitals signs should be taken before blood collection.

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

infusion, and at approximately 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.

9.3.6 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 ECHO or 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 will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The replicate ECG tracings should be obtained as closely as possible in succession. The full set of triplicates should be completed in less than 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 T-cell infusion and as long as deemed necessary by the Investigator.

In these participants with clinically significant cardiovascular risk factors, all reports of cardiac events following 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.

9.3.7 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 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.

9.3.8 Monitoring for Immune Effector Cell-Associated Neurotoxicity Syndrome

Brain MRI (or CT Scan if 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 if more than 4 months have elapsed since leukapheresis screening. Brain MRI may be performed as clinically indicated thereafter.

Immune Effector Cell-Associated Encephalopathy (ICE) 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 (if not excluded in the substudy) 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.

9.3.9 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 substudies.

9.3.10 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. Reference ranges for all safety parameters must be provided to the site by the laboratory responsible for the assessments.

9.3.11 Monitoring and Management of Replication-Competent Lentivirus (RCL) using Vesicular Stomatitis Virus G protein (VSV-G)

Replication Competent Lentivirus (RCL) is a potential risk associated with the use of lentiviral vectors; no RCL has ever been detected *ex vivo* or *in vivo*. The risk is derived from the detection of Replication Competent Retrovirus (RCR) during the use of early γ retroviral vector packaging systems which were inadequately designed to avoid recombination events between the vector and packaging components [Miller, 1990]. Updated γ retroviral packaging systems have not been associated with RCR. However, RCR/L must continue to be rigorously evaluated in vector and cell lots, and in participants post infusion [FDA, 2020a; FDA, 2020b; FDA, 2010].

Regulatory Agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a participant [FDA, 2020a; FDA,

2020b; FDA, 2010]. However, because the probability and characteristics of an RCL are unknown, no concrete plans have been put in place.

The following approaches have been discussed for participant management:

Provide targeted antiretroviral therapies based on genotyping of the RCL;

Intensive follow up of participant in consultation with FDA, and other Regulatory Authorities, National Institute of Health, gene therapy experts, study Investigators, and HIV physicians.

9.3.11.1 Testing for RCL in Clinical Studies

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

The lentiviral vector, whereby RCL testing will be performed on vector supernatant and end of production (EOP) cells by or under the direction of the manufacturing facility responsible for manufacturing and releasing the vector.

The T-cell product, whereby VSV-G qPCR testing will be carried out for release and biological RCL testing will also be performed.

Participant's PBMCs will be collected at timepoints indicated in the SoA within each substudy. If no gene modified cells are detected for 2 consecutive assessments post-infusion, and the participant is ≥2 years post infusion, RCL sample collection will discontinue.

If VSV-G deoxyribonucleic acid (DNA) copies are detected at any time point in the first year post-infusion, the safety monitoring protocol in Section 9.3.11.2 will be triggered. Participant's samples will continue to be tested for VSV-G DNA copies until VSV-G DNA copies are not detected for 2 consecutive annual assessments.

NOTE: The participant will continue to be followed by the Investigator by phone call or survey for up to 15 years post-infusion. If contact with the Investigator becomes no longer feasible, follow up can be transitioned to a local physician, preferably an oncologist.

9.3.11.2 Safety Monitoring Protocol

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

If the second test is positive, infusions for all participants receiving cells modified with the same vector lot will be postponed. The participant with the confirmed positive

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

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

9.3.12 Testing for Persistence of Transduced T cells and Insertional Oncogenesis

Peripheral blood mononuclear cells (PBMC) samples will be collected for monitoring persistence of gene modified cells. The samples will be tested using a DNA PCR-based method to detect the presence of the Psi gene, which is part of the lentiviral vector used to transduce T cells.

If no gene modified cells are detected for two consecutive assessments post infusion, and the participant is ≥2 years post infusion (for example, negative persistence assessments at year 4 and 4.5), monitoring will end including for other laboratory assessments such as hematology and chemistry. The participant will continue to be followed by the Investigator by phone call or survey for up to 15 years post-infusion. If contact with the Investigator becomes no longer feasible, follow up can be transitioned to a local physician, preferably an oncologist.

At the first instance of >1% of PBMCs testing positive for the Psi gene at or after 1 year post-infusion, the participant's PBMCs will be evaluated for integration site analysis. Integration site analysis assesses clonality and the possibility of insertional oncogenesis. While insertional oncogenesis is a potential risk in T cells transduced with a lentiviral vector, monitoring for it follows the recommendations set forth in the FDA and EMA guidances [FDA, 2020a; FDA, 2020b; EMA, 2009].

- If there is clonal dominance in the genetically modified T cell population (either monoclonality or oligoclonality), persistence and integration site assessment will be repeated within 3 months on a new sample. If the repeated analysis demonstrates: 1) persistent monoclonality, 2) evidence of insertional oncogenesis; OR 3) clonal expansion (an increase in percent predominance of a clone), there will be a review by GSK's SRT and Safety Governance Board to develop a monitoring plan specific to the health care risk, and strategies to inform participants, Investigators, FDA, and other regulators of the findings.
- If the integration site analysis indicates polyclonality of the genetically modified T-cell population, then study and persistence monitoring will continue as scheduled. Integration site assessment will only be repeated if there is a sudden increase in persistence or if there any suspicion/report of potential hematological malignancy.

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

9.4 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 (see substudies).

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 9.4.7. AESIs will be reported to Sponsor (Medical Monitor or designee) within 24 hours via e-mail (see SRM for further instructions).

Due to the nature of the treatment, participants are required to be followed for up to 15 years after treatment with genetically modified T cells according to FDA and EMA guidances [FDA, 2020a; FDA, 2020b; EMA, 2009]. 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:

- 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 a 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

If a participant is monitored in this protocol post disease progression (for example, in Substudy 2), s/he will only be monitored for delayed AEs.

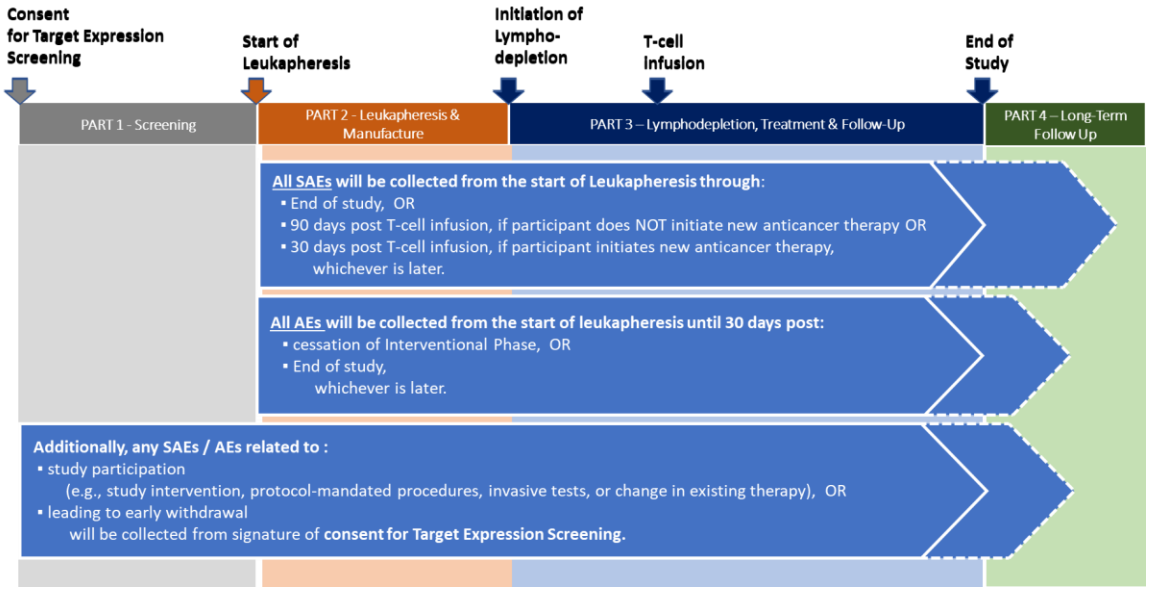
9.4.1 Time Period and Frequency for Collecting AE and SAE Information

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

- All SAEs will be collected from the start of leukapheresis until the end of study, or through 90 days following T-cell infusion if the participant does NOT initiate new anticancer therapy, or through 30 days following T-cell infusion if the participant initiates new anticancer therapy, whichever is later.
- All AEs will be collected from the start of leukapheresis until 30 days following cessation of interventional phase OR the end of study, whichever is later, at the time points specified in the SoA in each substudy.
- Additionally, any SAEs or AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or leading to early withdrawal will be collected in the AE section of the CRF from the time a participant signs the informed consent 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 case report form (CRF) not the AE section.

Figure 3 displays the AE/SAE collection time periods in relationship to the 4 phases of a substudy intervention.

Figure 3 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 9.4.7) 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 participant enrolls onto the LTFU 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 drug-related.

9.4.2 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.

9.4.3 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 9.4.7), will be followed until the event is resolved,

stabilized, otherwise explained, or the participant is lost to follow-up (as defined in the substudies). Further information on follow-up procedures is given in Section 12.3.

9.4.4 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

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

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.

9.4.5 Pregnancy

Should female participant or female partner of male participant become pregnant, collect details of pregnancy and report per guidelines in Section 12.4. Contraception period is mandated from the start of study intervention and defined as followed in Table 2, based on the study treatments received.

Table 2 Time Periods for Contraception Usage

Treatment 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
Lete-cel (GSK3377794)	A minimum of 12 months after lete-cel T-cell infusion. In the event that there is still evidence of persistence/gene modified cells in the participant's blood beyond 12 months, contraception to continue until notification by Sponsor that lete-cel 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.

Should female participant or female partner of male participant become pregnant, collect details of pregnancy and report per guidelines in Section 12.4. Should a female partner of a male participant be pregnant or 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.

9.4.6 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.

9.4.7 Adverse Events of Special Interest (AESIs)

Adverse events of special interest for this trial will be reported to Sponsor (Medical Monitor or designee) within 24 hours via email (see SRM for further instructions). The AESIs include but are not limited to:

- Cytokine release syndrome (CRS) [Note: Grade 3 or higher should be reported as SAE within 24 hours]
- Graft vs host disease (GvHD) [Note: Grade 3 or higher should be reported as SAE within 24 hours]
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grade 1 persisting beyond 24 hrs or associated with concurrent CRS; or Grade 2 or higher
- Guillain Barré syndrome (GBS) including acute inflammatory demyelinating polyneuropathy (AIDP) [Note: all cases must be reported as SAEs within 24 hours]

- Pancytopenia/aplastic anemia if any of the below events occur:
  - Occurs after the bone marrow reconstitution following the lymphodepletion regimen
  - Any Grade 3 or 4 cytopenia following lymphodepletion lasting more than 2 weeks with G-CSF support.
  - Requiring transfusion support (e.g. platelets or RBC) lasting more than 2 weeks following lymphodepletion
- Treatment-related inflammatory response at tumor site(s)
- Neutropenia Grade 4 lasting ≥28 days

9.5 Treatment of Overdose

NY-ESO-1 specific (c259) T cells must be administered as a single-dose 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 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 NY-ESO-1 specific (c259) T cells, any additional overdose considerations will be provided in the applicable substudy.

9.6 Pharmacokinetics

Pharmacokinetics of T cells (also known as T-cell expansion or persistence) in the peripheral blood will be measured in treated participants to evaluate 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 will be collected for measurement of transduced cell quantities; 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 9.3.12. Samples may be collected at additional time points during a substudy 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 related to concerns arising during or after the study.

T-cell pharmacokinetics in the peripheral blood will be measured in the participants to establish the relationship between persistence and response to NY-ESO-1 specific (c259) T cells. Persistence is also monitored as a long-term safety measure. The following methodology will be used to measure the cells:

- Quantitation of transduced cells by PCR of transgene from DNA extracted from PBMC

9.7 Pharmacodynamics

Serum cytokine levels and other biomarkers measured for research purposes (see Section 9.9) may be evaluated for pharmacodynamic relationships with NY-ESO-1 specific (c259) T-cell administration.

9.8 Genetics

Genetics research will be conducted on a genetics blood sample, plasma and tumor samples collected in the study as indicated in Section 9.9. Consent for Leukapheresis and Treatment encompasses consent for genetics research. See Section 12.5 for additional 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 Biomarkers

Collection of samples for biomarker research is also part of this study. Peripheral blood, serum, plasma, and tumor are required for biomarker research and will be collected as specified in the SoA within each substudy. These samples will be tested by the Sponsor or Sponsor's designee.

Biomarkers will be assessed to monitor biological parameters that may influence treatment outcome, including, but not limited to, immune cell phenotype, function, and expansion of the engineered infused T cells, as well as evaluation of candidate predictive biomarkers and their association with clinical response to treatment. Immune cell phenotyping will be assessed in the apheresis material, manufactured product, and post-infusion blood samples. Data from such studies will be correlated with clinical outcome.

As new technologies and data emerge, other novel biomarker tests involving DNA, RNA, or protein analysis relevant to the study objectives may be performed on consented blood, serum, plasma, and tumor samples.

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

Any consented samples collected may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to NY-ESO-1 specific (c259) T cells.

In addition, if consent for future research is obtained, leukapheresis product not utilized for cell manufacture may be used for research to improve manufacturing processes and analytical testing of adoptive T cell therapies.

With the participant's consent, samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study to enable further analysis of biomarkers in response to NY-ESO-1 specific (c259) T cells.

9.9.1 Tumor Biopsy

The efficacy of cancer immunotherapy is conditioned by the infiltration of tumors by activated tumor-specific T cells, the expression of target antigen, and the antigen processing machinery that enables surface expression of the antigenic epitope on the tumor cell surface. All of these are necessary for the activity of NY-ESO-1 specific (c259) T cells. The activity of these T cells will in turn be affected by an immunosuppressive or immune-potentiating environment in the tumor (e.g., regulatory T cells or helper T cells). Therefore, the direct evaluation of the presence of NY-ESO-1 specific (c259) T cells transduced cells, target antigen expression and processing machinery, and the "immune landscape" inside the tumor is of great value for understanding and optimizing cancer immunotherapy.

For this purpose, incisional, excisional, or core needle tumor biopsies are required. As listed in the inclusion criteria for lymphodepetion and treatment under each substudy, a biopsy collected prior to initiating lymphodepleting chemotherapy is mandatory. A newly obtained tumor biopsy is highly desirable and preferred, but if it is not feasible to obtain a fresh biopsy, archival tumor biopsy (FFPE block) taken after completion of the participant's last line of therapy may also be accepted. For participants who already provided a fresh biopsy for antigen expression and did not receive any bridging or standard of care intermediate anti-cancer therapy, the screening biopsy will be used for baseline. In addition, tumor biopsies at Week 4 (at the expected time of an active anti-tumor response by infused T cells) and at disease progression are also required.

Baseline and on-treatment tumor biopsies must be taken from non-target lesions. When possible, the same lesion(s) should be biopsied at both baseline and subsequent time points. The radiographic and/or clinical status of the biopsied lesion(s) should be documented at each time (e.g. decreased, stable, increased size or activity).

Tumor biopsy research studies may include but are not limited to:

Tissue expression of the target antigen NY-ESO-1 and/or LAGE-1a

- Infiltration of TCR engineered NY-ESO-1 specific (c259) T cells
- PD-L1 status
- Presence of immune suppressive or potentiating cells (including Treg, Myeloid Derived Suppressor Cells, M2 macrophages) and immune suppressive or potentiating environment (including TGFβ expression and signature)
- Protein analysis including immunohistochemistry or similar technologies to measure immune cell infiltrate and functional biomarkers
- RNA analysis including RNAseq, Nanostring, or similar technologies to measure immune cell infiltrate and signalling pathway biomarkers via gene expression profile (genetic analysis)
- Deep gene sequencing to assess T cell clonality through TCR Vbeta and/or Valpha sequencing (genetic analysis)
- Tissue analysis to determine the tumor mutational burden, evolution of tumor mutation profile over the course of therapy, microsatellite instability and genetic alterations by DNA sequencing (genetic analysis)

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

9.9.2 Liquid Biopsies (from circulating blood)

With an understanding on the limitations of collecting tumor biopsies which cannot always be obtained safely, liquid biopsies (peripheral blood plasma) are commonly used as surrogates to assess disease burden and response to the therapy. In addition to tumor biopsies, liquid biopsies will be collected (see SoA Table 3 of each individual substudy). These liquid biopsies may be used to extract circulating cell-free DNA (cfDNA), circulating tumor DNA (ctDNA) and exosomes. Analyses may include but are not limited to the following genetic research:

- Evaluation of expression of cancer testis antigens, including NY-ESO-1 and/or LAGE-1a.
- Evaluation of the global tumor mutational burden and genetic profiling of tumor specific genes (including NY-ESO-1 and/or LAGE-1a).
- Assessment and phenotyping of exosomes.

9.9.3 Cytokine Analyses

Serum is collected as specified in the SoA within each substudy. If cytokine release syndrome (CRS) is suspected, serum for cytokine analysis should be collected every day for the first week and approximately every other day thereafter until symptoms improve or an alternative diagnosis is confirmed (See Section 12.7). Details regarding serum collection are provided in the SRM.

Cytokines, growth factors and soluble receptors including but not limited to IL-6, IFNγ, TNFα, IL-2Rα, IL-10, IL-13, IL-1β, IL-1Ra, IL-8, IL-12, IL-15, IL-2, and GM-CSF, may be measured utilizing a multiplexed immuno-assay.

Measurement of the cytokine subset IL-1β, IL-10, IL-6, TNFα, and IFNγ is performed under Good Clinical Laboratory Practice (GCLP) conditions. All other measurements are exploratory.

9.9.4 Cell Phenotype and Functional Activity

A range of assays will be performed to elucidate the phenotype and activity of the cells collected from the apheresis (starting material), and of the gene-modified T cells (manufactured product) before and after infusion in the blood. The assays performed will depend upon availability of sample and clinical/scientific significance. The following assays may be included but are not limited to:

- Phenotype analysis for determination of T cell lineages by flow cytometry
- Quantitation of the activation status of immune subsets from PBMC by flow cytometry
- Analysis of gene expression profile to reflect activity of the cells
- Histologic evaluation of tumor-immune cell environment by single or multiplexed probe binding and microscopy.

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

9.9.5 Immunogenicity Assessments

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

Serum samples will be tested for anti-NY-ESO-1 specific (c259) T-cell antibodies 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 of 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 anti-NY-ESO-1 specific (c259) T-cell 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.

9.9.6 RNA Transcriptome Research

Transcriptome studies may be conducted using RNA-seq, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances

of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each tumor biopsy sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to the action of the NY-ESO-1 specific (c259) T cells.

The same samples may also be used to confirm findings by application of alternative technologies.

9.9.7 RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative reverse transcriptase polymerase chain reaction (RT-qPCR), Nanostring, or other methods, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in an RNA expression profile for each blood and tumor biopsy sample. The RNAs assayed may be those involved with the pathogenesis of synovial sarcoma or myxoid/round cell liposarcoma; or the action of NY-ESO-1 specific (c259) T cells. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to NY-ESO-1 specific (c259) T cells. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to the action of NY-ESO-1 specific (c259) T cells.

9.9.8 Genetic Blood Sample

A blood sample for DNA isolation will be collected from participants as specified in the SoA within each substudy. Genetic analysis may be conducted on this sample to investigate the relationship between genetic variants in the host and disease under study. The association of candidate or genome-wide genetic variants may be explored with efficiacy (ORR) and safety such as but not limited to cytokine release syndrome frequency/severity/duration.

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

In accordance with the FDA guidance [FDA, 2020a], all participants enrolled in this trial are asked to consider an autopsy and autopsies will be requested of the families for all participants who die during participation in studies after administration of gene transfer agents. To assure compliance, guidelines for performing an autopsy are provided in the SRM.

10 STATISTICAL CONSIDERATIONS

For each substudy, the objective (unless otherwise stated in substudy) is to evaluate whether NY-ESO-1 specific (c259) T cells, alone or in combination with other agents, improve the Overall Response Rate (ORR) over the standard of care for the specific tumor type and the target population. Response assessment for most solid tumors will be evaluated by RECIST v1.1 while all other tumors will use the appropriate established response criteria.

The sample size for each substudy of the protocol is chosen to adequately characterize the efficacy and safety data according to the objective of each substudy.

Definitions of populations for analyses and the statistical analyses for the primary/secondary endpoint are found in the substudies.

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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's 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
  - Reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., AAP) or health department guidelines.

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.
- For pediatric participants, the medical record must include a statement that legally authorized representative (parent/guardian) consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical Investigator determined that the person signing the ICF was the participant's legally authorized representative (parent/guardian). The authorized person obtaining the informed consent must also sign the ICF.
- Participants and, if applicable, their legally authorized representative (parent/guardian) must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- 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.

12.1.5 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.

12.1.6 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.

12.1.7 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 25 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.

12.1.8 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.

- Definition of what constitutes source data can be found in the Monitoring plan.

12.1.9 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.

12.1.10 Remote Monitoring and Source Data Verification

208467 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 ias 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 3 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 substudies for screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at all times indicated in the SoA in each substudy.
  - 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 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	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 and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	Chloride
	Albumin	Phosphorus	LDH	Urea[a]
		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 and estradiol (as needed in women of non-childbearing potential only)			

Laboratory Assessments	Parameters
	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c] • 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. 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 biomarkers HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1. The results of each test must be entered into the eCRF.

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = Aspartate aminotransferase; BNP = 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 pro-BNP; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cells; 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 Meeting 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 NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

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

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.

1. 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.

2. 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.

3. 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.
4. Is a congenital anomaly/birth defect
5. 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 or higher CRS 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 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 (including lete-cel) 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 following:

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.

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 or be withdrawn from the study.

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, stool and tumor biopsy per local regulations and IRB/IEC.
- DNA samples will be used for research related to NY-ESO-1 specific TCR (c259) 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 (c259) 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 (c259) 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 (c259) 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 Germline Control

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/calipers 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:

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, 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

- ≥15mm 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.

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 <u>not</u> assessed, sum of the diameters <u>cannot</u> 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 4 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 4 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 Lansky, Karnofsky, or 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 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 in each substudy 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 5]). 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. 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 in each substudy 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.

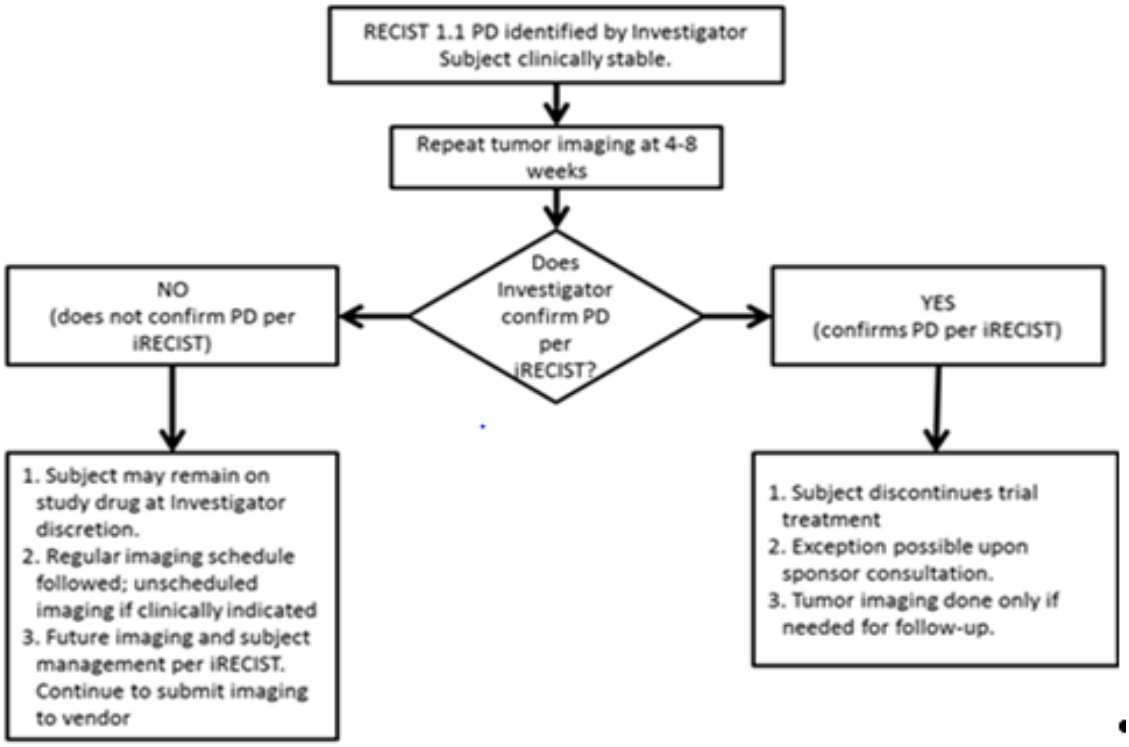
Additional details about iRECIST are provided in the iRECIST publication [Eisenhauer, 2009].

Table 5 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 4 Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



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 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.

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 include atovaquone (1500 mg daily with food in adults) or aerosolized pentamidine (300 mg every four weeks in adults for example, if sulfonamide allergy), or in accordance with institutional guidelines and labels.

12.7.2.2 Herpes Simplex,Varicella Zoster and Epstein-Barr Virus

All participants should receive prophylaxis with acyclovir (800 mg twice daily in adults) or valacyclovir (500 mg twice daily in adults) 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. 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 for adults include lamivudine (300 mg daily), entecavir (0.5 mg daily), or tenofovir (300 mg daily). Additional considerations will be left to Investigator's discretion in accordance with label recommendations and institutional guidelines.

12.7.2.5 Syphilis

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

12.7.2.6 Other Anti-Microbial Prophylaxis

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

If a participant 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 9.3.6).

12.7.3 Hematologic and Blood Product Support

Blood product support should be provided to maintain:

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

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

See AABB 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 ≥1.0 x 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

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 6 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below 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, 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 9.9.3.

If CRS is suspected, participants deemed to be with an increased burden of cardiovascular risk factors (per Section 9.3.6) might need 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 should 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 6 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 (e.g., 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 a patient without hypoxia for the possible neurologic compromise of a patient 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 be 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 30kg or above is 8mg/kg, administered intravenously over 1 hour with a total dose not exceeding 800mg 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 have been 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 7). Many of these symptoms can also occur in the setting of the preparative regimen, high dose cyclophosphamide, as well as with CRS. Any of these conditions including GvHD can be associated with fever. The skin is the most commonly involved organ, followed by the gastrointestinal (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 lete-cel program where we have the most clinical experience. Mild (Grade 1 or 2) transient transaminitis without cholestasis has been observed.

Table 7 Overview of Clinical Findings/Symptoms of GvHD

Organ	Findings/Symptoms	Differential Diagnosis	Histopathology
Skin	Maculopapular rash involving the neck and shoulders as well as the palms and soles that spreads to include the rest of the body.	Drug reactions, viral exanthems, CRS, and effects of chemotherapy or radiation	Apoptosis at base of epidermal rete pegs, dyskeratosis, exocytosis of lymphocytes, satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes and perivascular lymphocytic infiltration in the dermis.

Organ	Findings/Symptoms	Differential Diagnosis	Histopathology
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.

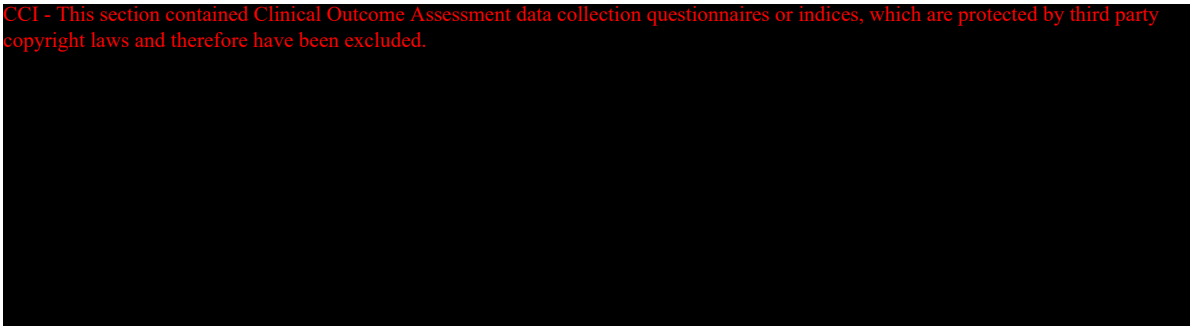
Management should include consultation with a physician with expertise in the management of participants following bone marrow transplant.

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 8. Careful measurement of stool volume and assessment of percentage of body area covered by rash are important for proper grading and treatment.

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



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

Table 9 Grading of Acute GvHD

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.

12.7.6.3 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 10 and should be considered in conjunction with input from the consulting physician with bone marrow transplant expertise.

Table 10 Management Guidelines for GvHD

Grade	Management Strategy
I	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.

Grade	Management Strategy
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 TCR (c259) engineered T cells. Bone marrow recovery following lymphodepletion will be defined as:

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

Aplastic anemia is a rare hematological disorder characterized by pancytopenia and a hypocellular marrow. 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.

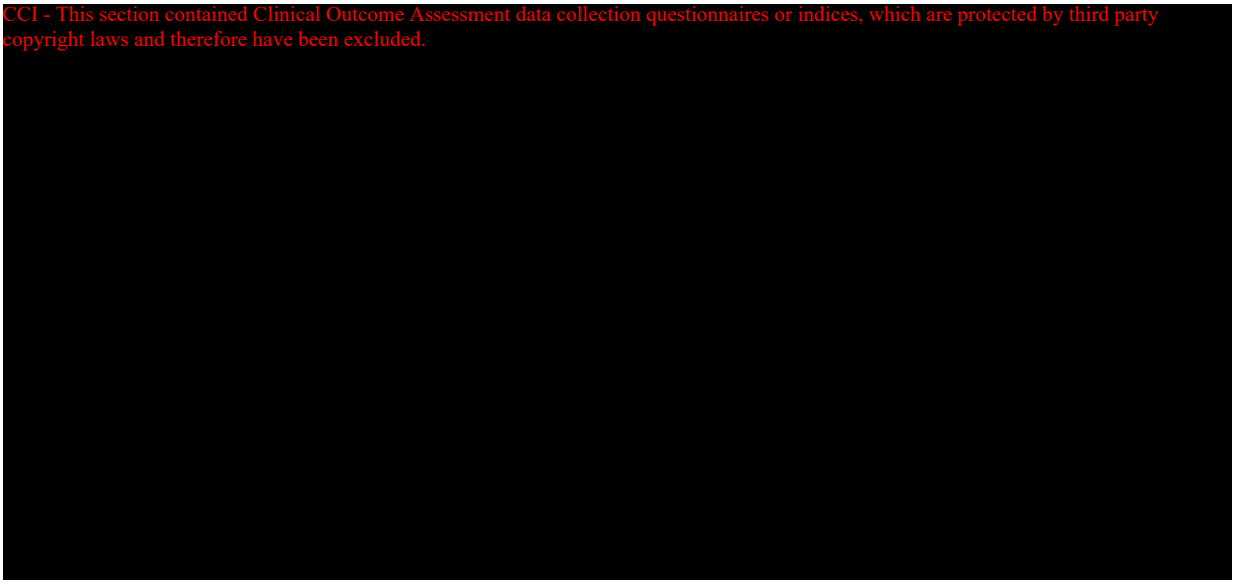
CRES occurring within the first 5 days after immunotherapy may be concurrent with high fever and CRS symptoms. This form of CRES tends to be of shorter duration, lower grade (Grade 1–2), and the CRS is generally reversible with anti-IL-6 therapy. CRES presenting as delayed neurotoxicity with seizures 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 11). Points are assigned for each of the tasks in Table 11, which are performed correctly. Normal cognitive function is defined by an overall score of 10. The ICE should be used to monitor all participants ≥12 years old for ICANS.

Table 11 Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool



While the 10-point ICE assessment is useful for screening adults for encephalopathy, its use in children may be limited to those who are ≥12 years with sufficient level of cognitive abilities to perform the ICE assessment. For children <12 years, the Cornell

Assessment of Pediatric Delirium (CAPD) (Table 12) is recommended to assist in the overall grading of ICANS. A CAPD score of ≥9 is suggestive of delirium and should be considered as Grade 3 ICANS. The CAPD score may also be used in patients >12 years with baseline developmental delay as it has been validated up to age 21. Other domains evaluated to grade ICANS in children are similar to those used in adults and include level of consciousness, motor symptoms, seizures, and signs of raised ICP.

Table 12 Encephalopathy Assessment for Children Age <12 Years Using the CAPD

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.

Abbreviations: CAPD= Cornell Assessment of Pediatric Delirium

The ICE score is used in grading of ICANS in adults as presented in Table 13. For children either ICE (≥12 years old) or CAPD (< 12 years old) scores are used as presented in Table 14.

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

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

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.

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

1. See Table 11 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.

Table 14 ICANS Grading for Children (Based on Lee, 2019)

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.

ICANS grade is determined by the most severe event (ICE or CAPD score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. Baseline CAPD score should be considered before attributing to ICANS.

1. A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
2. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
3. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
4. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

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

Brain MRI (or CT Scan if MRI not feasible) should be obtained for all participants at the time of screening: Baseline brain MRI must be obtained within 4 weeks prior to leukapheresis and should be repeated at Baseline visit prior to lymphodepletion only if more than 4 months have elapsed between last MRI and Baseline. Brain MRI may be performed at other time points, if clinically indicated.

ICE should be measured on the day of lete-cel infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures 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 15 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-reactive 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 15 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] IV 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 **Grades 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 **Grades 1, 2 & 3 PLUS** • Consider neurosurgical consultation for participants with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection

Abbreviations: CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; h = hour(s); ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome; ICU = intensive care unit; IL-6 = interleukin-6; IV = intravenous; MRI = magnetic resonance imaging.

1. Tocilizumab: 8mg/kg IV for patients weighing 30kg or above, administered over 1hr, max dose 800mg, doses at least 8hrs apart.

2. Consider dexamethasone 10 mg IV every 6 h (Grade ≤3 ICANS), or methylprednisolone 1 mg/kg IV every 24 h for 3days (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]

Grade 1 ICANS. Grade 1 ICANS is defined as a score of 7-9 on the ICE assessment for patients ≥12 years (Table 13) or a score of 1-8 on the CAPD assessment for patients

<12 years (Table 14). 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 patientshould be able to complete most of the ICE assessment. Grade 1 ICANS may be seen during CRS waxing and waning with febrile episodes.

Grade 2 ICANS. Grade 2 ICANS is defined as a score of 3-6 on the ICE assessment for patients ≥12 years (Table 13) or a score of 1-8 on the CAPD assessment for patients <12 years (Table 14). Expressive aphasia is the most specific first sign of severe neurotoxicity and early signs during Grade 2 include paraphasic errors (the production of unintended syllables and words during attempts to speak) and verbal perseveration with patients repeating the same words over and over. Patients with Grade 2 ICANS are able to communicate their needs but it is effortful. Patients may have depressed level of consciousness but are arousable to voice and the responses may be slowed.

Grade 3 ICANS. Grade 3 ICANS is defined as a score of 0-2 on the ICE assessment for patients ≥12 years (Table 13) or a score of ≥9 on the CAPD assessment for patients <12 years (Table 14). Patients with Grade 3 ICANS have severe global aphasia and are not speaking or following commands even when wide awake and therefore may be unable to complete any of the ICE questions. Alternatively, they may have excessive drowsiness and need tactile stimulus to attend to examiner. Any clinical seizure whether simple partial, complex partial or generalized, and any electrographic seizures would also meet criteria for Grade 3 ICANS (Table 13, Table 14). If neuroimaging shows new focal or local edema this would also be categorized as Grade 3 ICANS (Table 13, Table 14). 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. For patients <12 years, Grade 4 ICANS is defined as patients unable to perform CAPD. 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 (Table 13, Table 14). 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 (Table 13, Table 14). 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 (Table 13, Table 14).

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 Section 7.5.1 for details of prohibited medications.

12.7.9.1 Management of Neutropenia

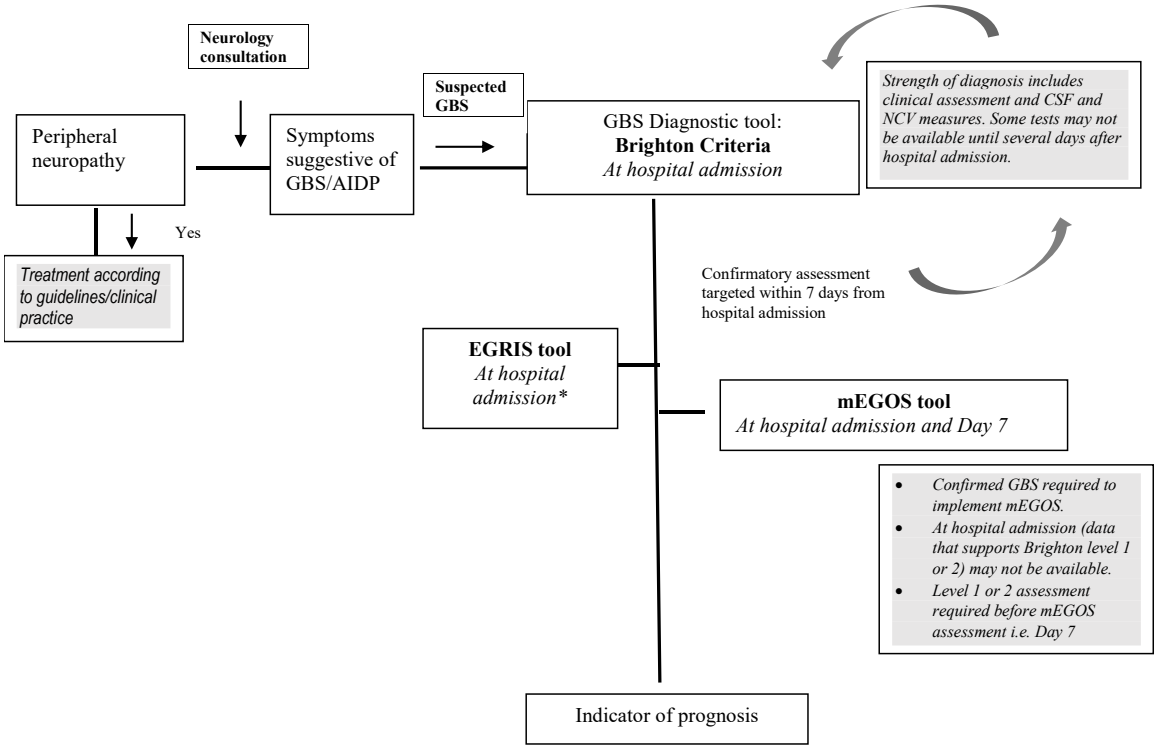
The conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF is recommended in all participants. G-CSF (e.g., filgrastim) should be used for management of neutropenia according to ASCO guidelines [Smith, 2015]. G-CSF must be given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

Long-acting (pegylated) G-CSF may be given in preference to short acting daily G-CSF in accordance with institutional standard practice. Pegylated G-CSF will be given as one dose ~24 hours post the final dose of cyclophosphamide(i.e. on Day -3).

12.7.10 Management of Guillain-Barré Syndrome (GBS)

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

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



**Please refer to algorithm for treatment described in Figure 5.*

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 GBS Respiratory Insufficiency Score (EGRIS)

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

Parameters required at hospital admission:

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

12.7.10.4 Modified Erasmus GBS Outcomes Score (mEGOS)

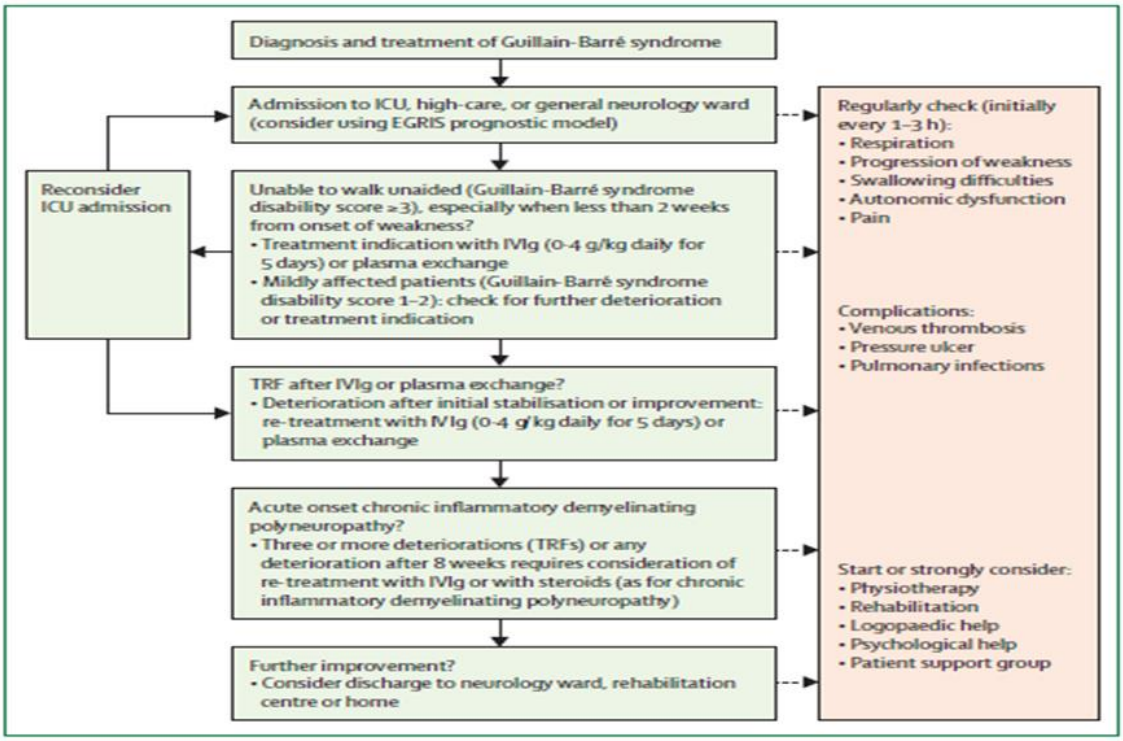
Parameters required at hospital admission and 7 days later [Walgaard, 2011]:

- 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 5) can be found in a review article on GBS [Willison, 2016].

Figure 5 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 16 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 16 Brighton diagnostic criteria

Brighton diagnostic criteria include assessment of the following:

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 *et al*,2014).

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].

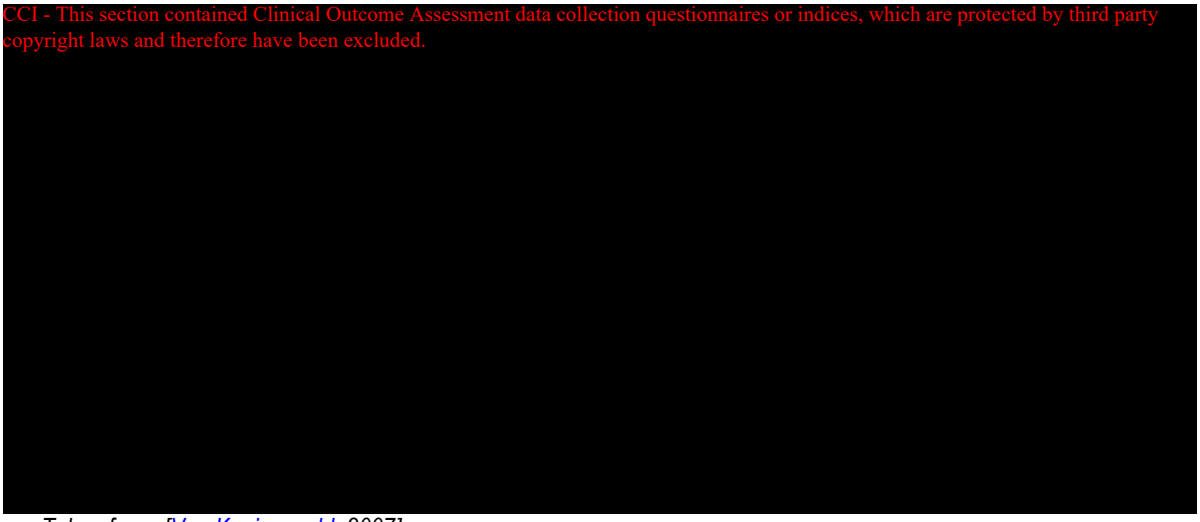
Please access link to assessment tool and record total score in eCRF.

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:



Taken from: [Van Koningsveld, 2007]

The MRC total scores range from 60 (CCI) to 0 (CCI). 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

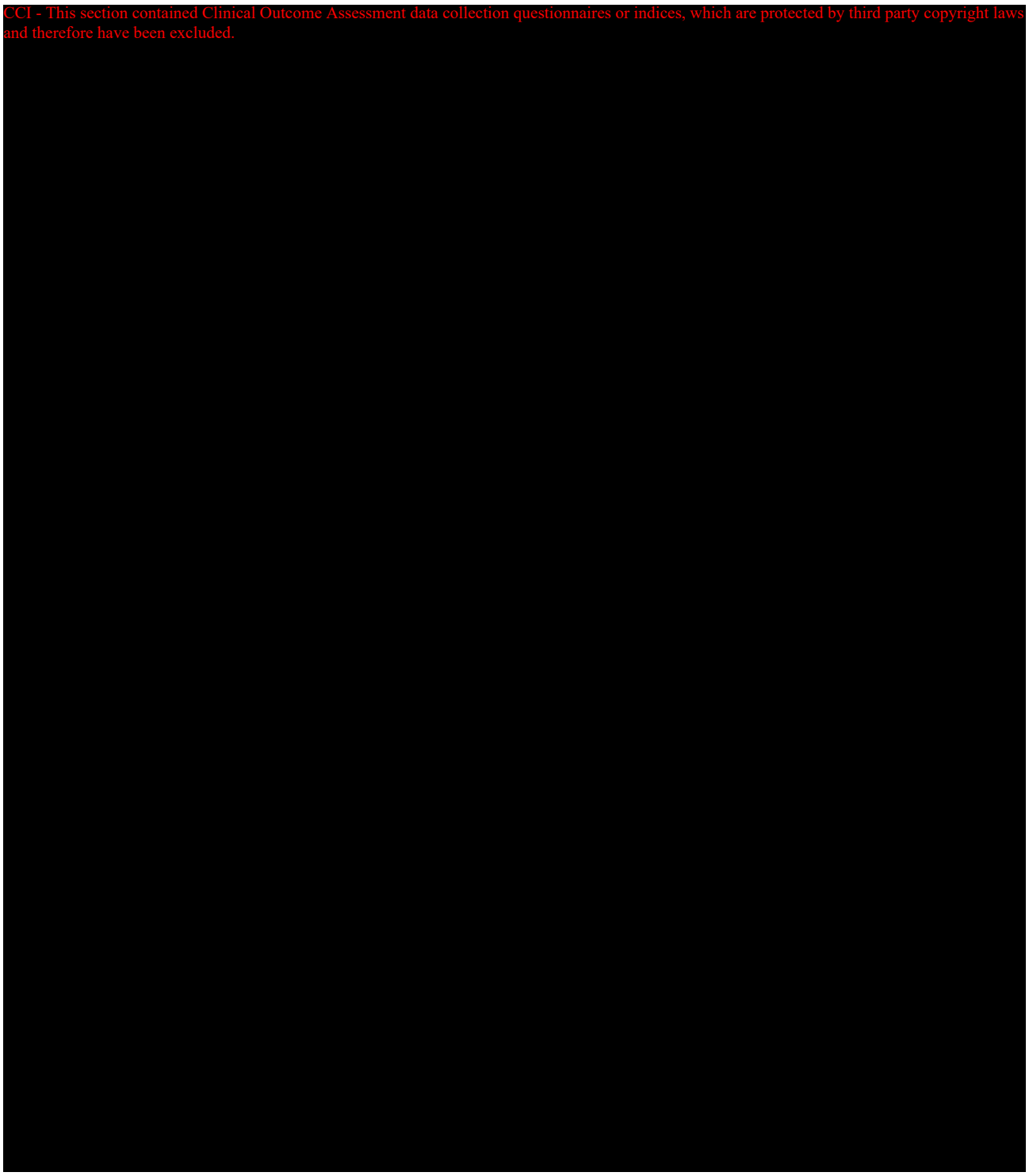
Please access link to assessment tool and record total score in eCRF.

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.

12.9 Appendix 9: Eastern Cooperative Oncology Group Performance Scale

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: Abbreviations and Trademarks

1L	First line
2L	Second line
AABB	American Association of Blood Banks
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
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
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
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
D	Day
dL	Decilitre
DCR	Disease control rate
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
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EMG	Electromyography
CCI [redacted]	
EOT	End of treatment
FACT	Functional assessment of cancer therapy
FACT-G	Functional assessment of cancer therapy – general
CCI [redacted]	
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FEV1	Forced expiratory volume in 1 second
FFPE	Formalin-fixed paraffin-embedded
FPCP	Female participants of child bearing potential
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
HPLC	High performance liquid chromatography
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
IND	Investigational new drug
INR	International normalized ratio
IO	Insertional oncogenesis
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
IVRS	Interactive voice response system
IWRS	Interactive web response system
kg	Kilograms
LAM	Lactational amenorrhoea method
LDH	Lactate dehydrogenase
Lete-cel	Letetresgene autoleucel (GSK3377794)
LTFU	Long-term follow-up
m^2	Meters squared
mAb	Monoclonal antibody
MCH	Mean corpuscular haemoglobin
MCV	Mixed cell volume
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mITT	Modified Intent to treat
mL	Millilitre
µL	Microliter
mm	Millimetres
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
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
PEAP	Primary Efficacy Analysis Population
PFS	Progression-free survival
PFT	Pulmonary function test
CCI	
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PT	Preffered term
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q12W	Every 12 weeks
QLQ	Quality of life questionnaire
QoL	Quality of life
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
RAP	Reporting and analysis plan
RBC	Red blood cell
RCL	Replication competent lentivirus
RECIST	Response evaluation criteria in solid tumors
RT-qPCR	Reverse transcriptase polymerase chain reaction
RNA	Ribonucleic acid
SAE	Serious adverse event
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
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
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
UPD	Unconfirmed progression
UPENN	University of Pennsylvania
VSV-G	Vesicular stomatitis virus G protein
W	Week
WBC	White blood cell
WHO	World health organization
WOCBP	Woman of childbearing potential

Trademark Information

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13 SUBSTUDIES

SUBSTUDY 1: LETETRESGENE AUTOLEUCEL (LETE-CEL, GSK3377794) IN NY-ESO-1 POSITIVE PREVIOUSLY UNTREATED ADVANCED (METASTATIC OR UNRESECTABLE) SYNOVIAL SARCOMA AND MYXOID/ROUND CELL LIPOSARCOMA

Substudy Title: Evaluation of Safety and Antitumor Activity of Lete-Cel (GSK3377794) in HLA-A2^{+} Participants with NY-ESO-1 Positive Previously Untreated Advanced (Metastatic or Unresectable) Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

TABLE OF CONTENTS

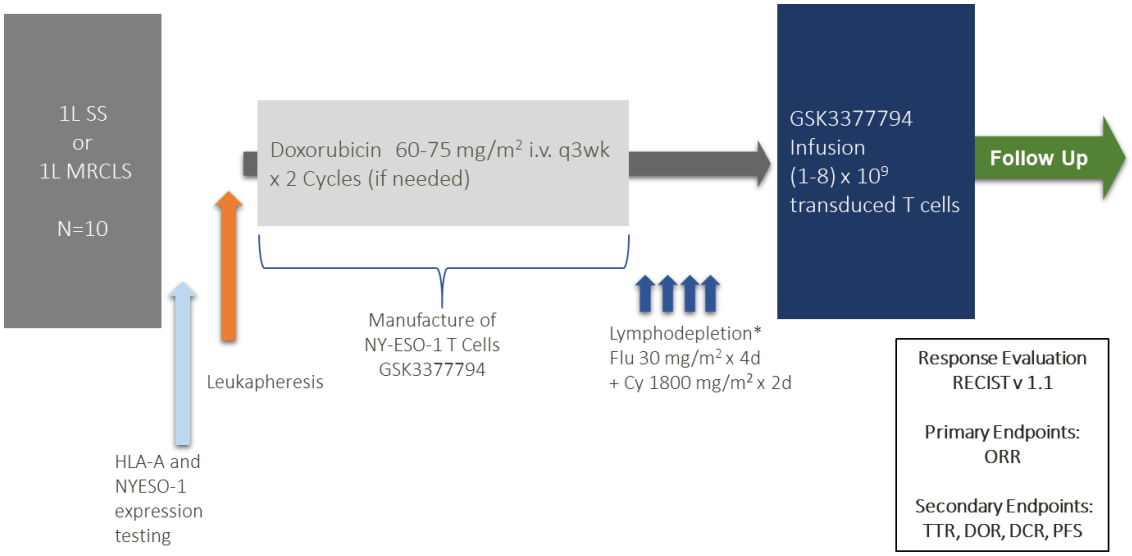
SUBSTUDY 1: LETETRESGENE AUTOLEUCEL (LETE-CEL, GSK3377794) IN NY-ESO-1 POSITIVE PREVIOUSLY UNTREATED ADVANCED (METASTATIC OR UNRESECTABLE) SYNOVIAL SARCOMA AND MYXOID/ROUND CELL LIPOSARCOMA

This previously untreated (first line, 1L) advanced (metastatic or unresectable) translocation-related sarcoma Substudy 1 contains substudy specific details. Refer to the body of the Core Protocol for all other information.

1 SYNOPSIS

This is a non-randomized substudy to investigate letetresgene autoleucel (lete-cel, GSK3377794) in previously untreated participants with advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma as defined in the inclusion criteria. In this substudy, we will not be evaluating tumors for LAGE-1a expression since the Immunohistochemistry assay used for the antigen detection recognizes NY-ESO-1 only and not LAGE-1a. LAGE-1a is rarely expressed in synovial sarcoma or myxoid/round cell liposarcoma.

Substudy 1 Design



* The lymphodepleting regimen is to be adjusted as described in Section 7.1.3 of this Substudy.

See Section 1 Synopsis in the core protocol for overall study summary.

2 SCHEDULE OF ACTIVITIES (SOA)

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments may be altered during the course of this substudy based on newly available data to ensure appropriate monitoring.

Table 1: Substudy 1 Schedule of Activities– Screening and Leukapheresis

	Screening Phase[1]			Notes
	Target Expression Screening[2]	Leukapheresis Eligibility Screening, within 28 days prior to leukapheresis[3]	Leukapheresis	
Informed Consent for Screening	X			1. Written informed consent must be obtained prior to performing any study assessments or procedures, except as stated in footnote 12. Informed Consent for Leukapheresis and Treatment must be repeated if given more than 90 days prior to leukapheresis procedure.
Informed Consent for Leukapheresis and Treatment[1]		X		
Inclusion/Exclusion for Screening	X			
Inclusion/Exclusion for Leukapheresis		X		2. This visit may be performed under a separate protocol when it is introduced.
Demographics	X			3. Participants must be HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 positive tumor prior to conducting leukapheresis eligibility screening procedures.
Central Lab HLA -A genotyping[3]	X			
Tumor expression of NY-ESO- 1[3]	X			
Liquid biopsy (blood)[4]	X			4. Only collect this sample if optional Genetics Research Consent has been signed by the participant. Sample may be collected any time from signature of optional consent until leukapheresis. Liquid biopsy is a blood sample from which circulating cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes may be extracted.
Medical History[5]	X	X		
Prior/Concomitant Medications[6]	X	X	X	
Height and Weight[7]		X		
Physical Exam (complete)		X	X[8]	
ECOG or Lansky or Karnofsky[10]	X	X		5. Medical history will be recorded in the eCRF at Target Expression Screening and at Lymphodepletion Screening/Baseline visits; however, any changes in medical history must be recorded in source documents throughout the conduct of the study.
Vital Signs[11]		X	X[8]	
12-lead ECG (in triplicate)		XXX	XXX[8]	
ECHO/MUGA		X[12]		6. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.
CT / MRI		X[13]		
Brain MRI[14]		X[13]		7. In pediatric participants height and weight will also be evaluated as a percentile vs national growth charts (based on sex and age) and vs genetic height target (expected height based on parental heights) and evaluation will be performed on whether growth is normal or abnormal.
Hematology		X[12]	X[8]	
Clinical Chemistry		X[12]	X[8]	
Coagulation Tests		X[12]	X[8]	
Lymphocyte Subset (CD3/CD4/CD8)		X[8]	X[8,9]	8. To be performed within 7 days prior to the day of leukapheresis.
Estradiol and FSH, if needed to determine CBP		X		9. CD3 count prior to leukapheresis should be preferably performed within 24 hours from leukapheresis procedure.
Pregnancy Test[15]		X[15]	X[15]	10. Lansky will be used for participants <16 years of age; Karnofsky will be used for participants ≥16 and <18 years of age; and ECOG will be used for participants ≥18 years of age.
Urinalysis		X[12]	X[8]	
Infectious disease markers[16]		X[12]		

	Screening Phase[1]			Notes
	Target Expression Screening[2]	**Leukapheresis Eligibility Screening, within 28 days prior to leukapheresis[3]**	**Leukapheresis**	
Creatinine clearance by GFR or 24h urine[17]		X		11. Includes temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. 12. ECHO/MUGA and laboratory assessments performed as standard of care prior to study consent will be acceptable as long as assessment is done within 28 days before leukapheresis. 13. CT/MRI scan performed as standard of care prior to study consent will be acceptable as long as assessment is done within 90 days before leukapheresis. Any FDG PET/CT performed as part of clinical routine within 90 days before leukapheresis, will also be collected. 14. In addition to the Brain MRI, MRI of the spine will be performed when clinically indicated. 15. WOCBP must have a highly sensitive negative urine or serum pregnancy test at screening for leukapharesis and within 24 h prior to leukapheresis. 16. Includes HIV, HBV, HCV, HTLV, EBV, CMV, and syphilis (spirochaete bacterium). 17. See Section 6.1 Table 5 for specifics on renal assessment. 18. SAEs and Aes assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or leading to study withdrawal will be collected from signing informed consent for target expression screening. All SAEs and Aes will be collected starting at leukapheresis (See Section 9.4.1 in the Core Protocol).
Adverse Events and Serious Adverse Events	X[18]	X[18]	X	
Leukapheresis			X	

AE=adverse event; CBP=child-bearing potential; CT = computerized tomography; EBV = Epstein Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FDG = Fluorodeoxyglucose; FSH=follicle-stimulating hormone; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; MRI = magnetic resonance imaging; MUGA = multigated acquisition; SAE=serious adverse event; WOCBP = Women of childbearing potential.

Table 2 Substudy 1 Schedule of Activities – Interventional Phase (Lymphodepletion and Treatment)

	Treatment Fitness & Eligibility / Baseline	Lymphodepletion				T-cell Infusion[1]	Post T-cell Infusion												
Month (1 month = 4 weeks)	-1					1								2				3-6	Q3M from month 9 until confirmed PD
Week (Week N visit for N≥1 is scheduled on 1st day of the week = Day 7N-6)	-3 to -2	-1				1					2	3	4	5	6	7	8	10, 12, 18, 24 or until confirmed PD, whichever is sooner	
Day	-17 to -8	-7	-6	-5	-4	1	2	3	4	6	8	15	22	29	36	43	50	64, 78, 120, 162	
Visit Window	N/A								±1 day					±3 days				±7 days	±1 month
Treatment Fitness and Inclusion/Exclusion for Treatment Eligibility	X																		
Request lete-cel shipment	X[2]																		
Med. History[3]	X																		
Physical Exam (complete)	X	X				X	X	X	X	X	X		X			X	X	X	X
Physical Exam (dedicated)												X		X	X				
Prior/Con Meds[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG, Karnofsky or Lansky[5]	X					X					X		X		X		X	X	X
Developmental exam, height, and puberty assessment[6,7]	X																		X[8]
Vital Signs[9] and weight[7]	X	X	X	X	X	X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECHO/MUGA[11]	X																		
Pulse oximetry						X[12]	X	X	X	X	X	X[13]	X	X[13]		X	X	X	
12-lead ECG[14]	XXX					X			X		X								

	Treatment Fitness & Eligibility / Baseline	**Lymphodepletion**				**T-cell Infusion[1]**	**Post T-cell Infusion**												
Month (1 month = 4 weeks)	**-1**					**1**								**2**				**3-6**	**Q3M from month 9 until confirmed PD**
Week (Week N visit for N≥1 is scheduled on 1st day of the week = Day 7N-6)	**-3 to -2**	**-1**				**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**	
Day	**-17 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**6**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**64, 78, 120, 162**	
Visit Window	**N/A**								**±1 day**					**±3 days**				**±7 days**	**±1 month**
CT/MRI[15]	X														X			X[16]	X[16]
Brain MRI[17]	X[17]																		
ICE or CAPD[18]						X[19]	X	X	X	X	X								
Chest X-Ray	X																		
Hematology[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Uric acid	X					X										X			
Creatinine clearance by GFR or 24 h urine[21]	X																		
Coagulation Tests[20, 22]	X					X	X	X	X	X	X	X							
Ferritin[20]	X																		
Troponin and NT-proBNP / BNP test[23]	X																		
Pregnancy	X					X[24]							X				X	X[25]	X[25]
Urinalysis[26]	X		X	X	X														
Infectious disease markers[27]	X																		
CMV IgG and PCR[28]	X					X						X		X		X			
Thyroid function tests	X																		
CRP[20]	X					X			X		X	X	X	X	X	X	X	X	X

	Treatment Fitness & Eligibility / Baseline	**Lymphodepletion**				**T-cell Infusion[1]**	**Post T-cell Infusion**												
Month (1 month = 4 weeks)	**-1**					**1**								**2**				**3-6**	**Q3M from month 9 until confirmed PD**
Week (Week N visit for N≥1 is scheduled on 1st day of the week = Day 7N-6)	**-3 to -2**	**-1**				**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**	
Day	**-17 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**6**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**64, 78, 120, 162**	
Visit Window	**N/A**								**±1 day**					**±3 days**				**±7 days**	**±1 month**
Adverse Events and Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transgene Copies (Persistence for Safety) and VSV-G DNA (RCL)[29]	X																	Week 12 and 24	Month 12 and Q6M[30]
Genetic sample	X																		
Survival follow-up																		X	X
Lymphodepletion																			
Fludarabine		X[31]	X	X	X														
Cyclophosphamide			X	X	X														
Investigational Product Administration																			
Lete-cel (GSK3377794)						X													
Patient-Reported Outcomes[32]																			
Post-lete-cel infusion interview (adult participants only)											X[33]								
EOT interview (adult participants only)																			X[34]
CCI																			

	Treatment Fitness & Eligibility / Baseline	Lymphodepletion				T-cell Infusion[1]	Post T-cell Infusion												
Month (1 month = 4 weeks)	-1					1								2				3-6	Q3M from month 9 until confirmed PD
Week (Week N visit for N≥1 is scheduled on 1st day of the week = Day 7N-6)	-3 to -2	-1				1				2	3	4	5	6	7	8	10, 12, 18, 24 or until confirmed PD, whichever is sooner	
Day	-17 to -8	-7	-6	-5	-4	1	2	3	4	6	8	15	22	29	36	43	50	64, 78, 120, 162	
Visit Window	N/A								±1 day					±3 days				±7 days	±1 month
CCI	[redacted]																		

1. On Day 1, all samples will be collected and assessments performed prior to T-cell infusion (within 24 h), unless otherwise specified.
2. As lete-cel needs to be on site prior to lymphodepletion, request lete-cel no later than 4 working days prior to the day of lymphodepletion. The mechanism of request will be provided in and the Drug Product and Infusion Manual.
3. Medical history will be recorded in the eCRF at Treatment Eligibility Screening / Baseline visit; however, any changes in medical history must be recorded in source documents throughout the conduct of the study.
4. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.
5. Lansky will be used for participants <16 years of age; Karnofsky will be used for participants ≥16 and <18 years of age; and ECOG will be used for participants ≥18 years of age.
6. To be assessed in pediatric participants only.
7. In pediatric participants height and weight will also be evaluated as a percentile vs national growth charts (based on sex and age) and vs genetic height target (expected height based on parental heights) and evaluation will be performed on whether growth is normal or abnormal.
8. To be assessed once a year.

9. Vital signs include temperature, blood pressure, pulse rate, and respiratory rate.
10. Vital signs on day of T-cell infusion should be taken pre-infusion, and approximately at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
11. If suspected CRS Grade ≥2, an ECHO/MUGA is required at onset of Grade ≥2 CRS. Additional monitoring must be conducted (including inpatient continuous cardiac telemetry monitoring) for a minimum of 3 days post onset and as long as deemed necessary by the Investigator (refer to Section 12.7.5).
12. On T-cell infusion day, pulse oximetry should be taken pre-infusion, and at approximately 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
13. Pulse oximetry at these visits will be performed if medically indicated.
14. ECG can also be performed at other time points if medically indicated. Triplicate ECG will be collected at Treatment Eligibility Screening / Baseline visit and single ECGs at other timepoints. Participants with an increased burden of cardiovascular risk factors (as per Section 9.3.6) will undergo evaluation by a cardiologist prior to lymphodepletion.
15. See Section 9.1.1 in the core protocol for scan description and areas to scan. If a participant is found to have a tumor response or PD by imaging and considered to be clinically stable by iRECIST criteria (see Section 12.6.2), a follow-up confirmation scan must be done no earlier than 4 weeks and no later than 8 weeks following the scan when response or PD first seen. A participant is not considered to have a response or PD until follow-up scan confirms the finding.
16. CT/MRI will not be performed at Week 10. CT/MRI assessments only need to continue until confirmed PD.
17. Brain MRI should be performed at baseline if more than 4 months have elapsed from last MRI. Brain MRI will be performed at other time points, if clinically indicated. MRI of the spine will be performed, if clinically indicated.
18. All participants will be monitored as shown in the SoA. 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. It can also be used at later visits if indicated. In participants < 12 years of age, CAPD should be used in place of ICE.
19. To be administered prior to T-cell infusion.
20. If CRS and/or ICANS is suspected, chemistry, hematology, ferritin, coagulation and CRP tests should be performed locally every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed. In addition, if CRS is suspected, cytokine samples will be collected for central analysis following same schedule (as per SOA Table 3 footnote 4).
21. See Section 6.1 Table 5 for specifics on renal assessment.
22. Coagulation tests include INR, PTT or aPTT and fibrinogen. Coagulation tests should be taken at baseline, Day 1, 2, 3, 4, 6, 8 and 15.
23. Troponin and NT-proBNP / BNP tests should be monitored for participants with CRS Grade ≥2 as clinically indicated.
24. WOCBP must have a negative urine or serum pregnancy test prior to lete-cel infusion.
25. WOCBP will need to have pregnancy tests performed at all visits indicated in the table for the duration of the contraception period (Section 6.1 of this Substudy).
26. In addition to the specified time points, urinalysis will be done at other timepoints if warranted by the symptoms.
27. Includes HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochaete bacterium).
28. Only participants who are CMV positive at Baseline will continue to be monitored for CMV viremia. CMV will also be assessed if GBS is suspected.
29. If possible, this sample also needs to be obtained in case of any SAE that occurs after T-cell infusion, unless the sample has been collected recently due to a scheduled visit assessment.
30. If no gene modified cells are detected for two consecutive assessments post-infusion, and the participant is ≥2 years after T-cell infusion, samples for VSV-G DNA (RCL) and persistence of gene modified cells will be discontinued (Section 9.3.11.1 of the Core Protocol).
31. On Day -7 fludarabine will not be administered to participants ≥60 years old.
32. Patient-Reported Outcomes instruments are only for adult participants.

33. Contact participant about one week after T-cell infusion to schedule the phone interview to be conducted by Day 21 of the study. If phone interview cannot be scheduled at this time, contact participant every two weeks until successful or the 60-day limit is reached from T-cell infusion. Beyond 60 days from T-cell infusion, no need to conduct the participant interview as recall may not be reliable.
34. To be conducted within approximately 21 days following the last study visit.
35. To be administered prior to infusion.

BNP = B-type natriuretic peptide; CAPD = Cornell Assessment of Pediatric Delirium; CMV = Cytomegalovirus; Con Meds = concomitant medications; CRS=cytokine release syndrome; CT = computerized tomography; EBV = Epstein Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; CCI [redacted] EOT = end of treatment; CCI [redacted]; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE=Immune Effector Cell-Associated Encephalopathy; Med history=medical history; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NT-proBNP = N-terminal pro-BNP; PCR = Polymerase chain reaction; PD=progressive disease; CCI [redacted]; CCI [redacted]
Q3M = every 3 months; RCL=replication competent lentivirus; TSH = Thyroid stimulating hormone; VSV-G =vesicular stomatitis virus G protein; WOCBP = Women of childbearing potential

Table 3 Substudy 1 Schedule of Activities – PK, Immunogenicity and Biomarkers (Interventional Phase)

	Sample Type	Baseline	Lymphodepletion				T-cell infusion					Post T-cell infusion							
Month (1 month = 4 weeks)		-1					1								2			3-6	Q3M from month 9 until confirmed PD[1]
Week		-3 to -2	-1				1					2	3	4	5	6	8	(10) [2], 12, 18, 24 or until confirmed PD, whichever is sooner[1,2]	
Day		-17 to -8	-7	-6	-5	-4	1[3]	2	3	4	6	8	15	22	29	36	50	(64) [2], 78, 120, 162	
Visit Window		N/A								±1 day					±3 days			±7 days	±3 months
Cell phenotype and Functional Assays	PBMC	X								X		X	X	X		X	X	X	X
Transgene Copies (Persistence)	PBMC	X					X	X		X		X	X	X		X	X	X	X
Cytokine Analyses[4]	Serum	X					X	X	X	X	X	X	X	X		X	X	X	X
TGF-β analyses	Plasma	X					X					X	X	X		X		X	X
Anti-lete-cel Antibodies	Serum						X						X			X	X	Week 12, 24	Month 9, 12, 18, 24, 30, 36
Liquid biopsy (blood)[5]	Plasma	X										X		X		X		X	X
Tumor Biopsy[6]	Biopsy	X[7]												X[8]				X[9]	

1. All assessments need to be performed at all visits specified in the Table, up to the visit establishing confirmed PD or study withdrawal or discontinuation.
2. Assessments should match imaging (Body CT/MRI) visits; consequently PK, immunogenicity and Biomarker samples will not be collected at Week 10.
3. All assessments to be performed prior to T-cell infusions

4. If CRS is suspected, serum for cytokine analysis should be collected for research every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.
   Notes:
   - For scheduled visits where a cytokine sample collection is already requested, there is no need to collect an additional sample from the CRS collection kit that day.
   - Chemistry, hematology, ferritin, coagulation and CRP tests should also be performed locally following same schedule (as per SOA Table 2 footnote 20).
5. Blood sample from which circulating cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes may be extracted.
6. Biopsies for research are at Baseline, at Week 4, and at disease progression with the exception of participants for whom there is no safely accessible tumor tissue. In addition to the indicated collection times, tumor biopsies can be obtained at any time during the study execution.
7. The Baseline biopsy should be collected anytime within 90 days prior to the start of lymphodepleting chemotherapy An archived FFPE block from a biopsy preferably taken 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).
8. Week 4 biopsy must be taken preferably from D21 if medically feasible, but window for collection is extended until Week 6 visit (D39).
9. Must be taken once at disease progression if medically feasible.

PBMC=peripheral blood mononuclear cell; PD=progressive disease; Q3M = every 3 months

Table 4 Substudy 1 Schedule of Activities – Follow-up post Completion of Interventional Phase and before transition to Long-Term Follow-up protocol (208750)

Substudy 1: Completion of Interventional Phase Follow-up[1]												
Time post lete-cel infusion	**Year 1 [2]**			**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Years 6-15 [3]**
Months (1 month = 4 weeks)	3	6	12	18	24	30	36	42	48	54	60	Annually
Visit window	± 2 weeks		± 3 months									± 6 months
Safety Assessments												
Medical History, Tobacco Use, and Physical Exam [4]		X	X	X	X	X	X	X	X	X	X	X
Mutagenic agents, other investigational agents or anti-cancer therapies		X	X	X	X	X	X	X	X	X	X	X
Adverse Events and Serious Adverse Events [5]		X	X	X	X	X	X	X	X	X	X	X[6]
Pregnancy test for WOCBP [7]	<==========X[7]==========											
Haematology [8]		X	X		X		X		X		X	
Serum chemistry [8]		X	X		X		X		X		X	
Laboratory Assessments												
Transgene Copies (Persistence) for safety association VSV-G DNA (RCL) for safety [8,9]		X	X	X	X	X	X	X	X	X	X	X[9]
Other Assessments												
Survival Status [10]		X	X	X	X	X	X	X	X	X	X	X

1. If a site visit is not feasible, then medical evaluation of participants may take place via telemedicine (e.g. phone call or video conferences) where country and/or local regulations allow. Where applicable country and local regulations and infrastructure for home healthcare allow, upon approval by the sponsor, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include medical history, physical exam, collection of blood samples, measurement of height and weight. Remote visits may be performed upon approval by the sponsor at the participant's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary.
2. Assessments for the Year 1 will be conducted per Table 2 and Table 3 until disease progression.
3. Participants who do not have persistence of gene modified cells may be followed remotely during years 6-15.
4. New medical history/medications/chemotherapies.

5. Adverse Event and Serious Adverse Event collection is limited to:
    a. New malignancies
    b. New incidence or exacerbation of a pre-existing neurologic disorder
    c. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
    d. New incidence of a hematologic disorder
    e. New incidence of infection (potentially related to gene-modified cell therapy)
    f. Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy
6. During years 6-15 of annual follow-up period, AEs and SAEs will be entered in the CRF if reported by the participants or investigator.
7. For Women of child bearing potential (WOCBP), pregnancy testing should be conducted during contraception period only. When pregnancy testing is performed at visits where haematology sample is collected, blood pregnancy testing will be done. At visits where haematology sample is not collected, urine pregnancy test is acceptable unless serum testing is required by local regulation or IRB/IEC.
8. If a visit for medical evaluation is conducted via telemedicine, a site visit to collect a blood samples should be performed as soon as practicable.
9. If no gene modified cells are detected for 2 consecutive assessments post infusion and the participant is ≥2 years post T-cell infusion, all laboratory assessments including persistence and RCL may be discontinued (Section 9.3.12 of the Core Protocol).
10. If a participant is contacted between the scheduled visits, the date of last contact should be recorded as an unscheduled visit.

Abbreviations: RCL=replication competent lentivirus; VSV-G =vesicular stomatitis virus G protein

3 INTRODUCTION

3.1 Background and Rationale for First Line Therapy with Lete-cel (GSK3377794)

Background

See Core Protocol Section 3.2 for background information on TCR approach, NY-ESO-1, and letetresgene autoleucel (lete-cel, GSK3377794).

For evaluation of lete-cel in translocation-related sarcomas of synovial sarcoma (SS) and myxoid/round cell liposarcoma (MRCLS), this substudy will enroll 10 first line participants with advanced (metastatic or unresectable) SS or MRCLS. This substudy will start with the clinical drug product supply and may use the intended commercial drug product supply once it is available and the regulatory document has been amended to support this supply. The change from clinical to intended commercial drug product supply will include a different manufacturing platform for T cell selection and activation and other appropriate changes in line with the phase of development.
This Substudy has been designed to generate safety and efficacy data for lete-cel in participants ≥10 years of age who have previously untreated advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma expressing the NY-ESO-1 antigen, who are HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06 allele positive.

Rationale

Soft Tissue Sarcomas (STS) are a heterogeneous group of connective tissue cancers originating from mesenchymal cells and their precursors [Blay, 2014] representing ~1% of all cancers in adults worldwide each year and accounting for ~2% of cancer related mortality [Singer, 2000; Amankwah, 2013]. STS consists of approximately 50 histological subtypes [Amankwah, 2013], each with distinct specific characteristics, including differential chemo-sensitivity.

Synovial Sarcoma:

Synovial sarcoma is a rare malignancy accounting for approximately 5–10% of all STS [Riedel, 2018; Noone, 2018; Brennan, 2016; Honoré, 2015]. The estimated incidence of synovial sarcoma is 0.15 per 100,000 in the US and 0.14 per 100,000 in the UK [Wang, 2017; Stacchiotti, 2018; Brennan, 2016]. Approximately one-third of synovial sarcoma occurs in childhood, with a peak incidence in the third decade of life [Ferrari, 2008]. The European Paediatric Soft Tissue Sarcoma Study Group conducted a prospective trial exploring the incidence and outcome of synovial sarcoma in European patients [Ferrari, 2015]. From August 2005 to August 2012, 138 patients <21 years old with synovial sarcoma were registered from 60 centers in 9 European countries. The median age at diagnosis was 13.7 years. Of the 138 participants included in this study, 29 (21%) were <10 years of age and 109 (79%) were ≥10 years of age.

Synovial sarcoma is a life-threatening disease. Although 5-year overall and cancer-specific survival of adult patients diagnosed with synovial sarcoma is about

50-60%, the outcome of patients who develop metastatic disease is dismal [Spillane, 2000; Lewis, 2000; Singer, 2000]. Approximately 50% of patients with synovial sarcoma will develop metastatic disease [Ten Heuvel, 2009; Krieg, 2011], and the survival for patients developing metastatic disease is approximately 12-15 months with current treatment options.

Current standard treatments for patients with metastatic synovial sarcoma are suboptimal and provide no survival benefit.

Standard first-line (1L) treatment for patients with advanced unresectable, or metastatic synovial sarcoma consists of anthracycline chemotherapy as single agent or as a combination regimen with alkylators (e.g., doxorubicin with ifosfamide). These chemotherapy regimens have response rates ranging between 18-30% in the reported series [Spurrell, 2005; Sleijfer, 2010; Vlenterie, 2016], with an average durability of response less than 6 months.

Two years ago, Lartruvo (olaratumab) received accelerated FDA approval as 1L treatment in combination with doxorubicin for metastatic soft tissue sarcoma (STS) [Lartruvo USPI, 2016]. However, recently the confirmatory trial (ANNOUNCE study) did not demonstrate any survival benefit nor any improvement in response rates (18%) over standard chemotherapy, and therefore, the study failed to meet its primary endpoint [Tap, 2019]. Accordingly, the approval for this agent has been recended in the US and EU. A review of the medicine has now been initiated by the regulators (US/EU) and its approval status has been rescinded. Other targeted agents such as pazopanib and trabectedin in the second line setting have also not demonstrated an improvement in survival and responses with these agents remain low (6-13%). These data highlight the ongoing unmet medical need in metastatic soft tissue sarcomas. Novel therapies are needed that are sarcoma subtype-specific, and biomarker driven studies are needed to improve survival in this disease.

From the immunological perspective, synovial sarcomas are considered “cold tumors”, and have not demonstrated any responses to checkpoint inhibitor therapies in studies evaluating these as single agents or in combination approaches with vaccines or other agents [Maki, 2013; Patnaik, 2015; NCT02609984; NCT01643278; NCT02304458; NCT02428192; NCT02301039; NCT02500797; NCT02636725; NCT02331251].

Myxoid/Round Cell Liposarcoma (MRCLS):

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

accordance with the WHO 2013 classification [IARC WHO Classification of Tumours, No 5, Fletcher 2013].

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

Myxoid tumor types have relatively favorable prognoses, with an ~80-90% 5-year survival rate but tumors with a round-cell component >5% have a poor prognosis with a 5-year survival rate of ~50-75% because they recur locally and tend to metastasize quickly and widely [Smith, 1996]. The median time from diagnosis to metastases is 35 months.

Treatment involves the wide surgical excision of the tumor and surrounding tissue ; high-grade round cell liposarcoma may be treated with pre-operative chemotherapy and/or pre-operative or post-operative radiotherapy [NCCN, 2012]. Radiotherapy decreases the incidence of local relapse but chemotherapy may not prevent metastatic occurrence nor improve survival [Moreau, 2012; Hoffman, 2013].

Doxorubicin and ifosfamide are usually first line treatment options for metastatic disease. Retrospective analyses in previously untreated patients demonstrated response rates of ~38-45% [Jones 2005; Katz, 2012]. In a recent retrospective study in the United States on 350 patients, median OS and median PFS from start of first-line therapy for MRCLS was 29.9 months (95% CI, 27-44.6) and 8.9 months (95% CI 4.5-12.0) [Pollack, 2020].

It has been recognized that a proportion of patients with soft tissue sarcomas, and up to 76% of synovial sarcomas, express high levels of the cancer testis antigen NY-ESO-1 [Lai, 2012] which is known to be immunogenic [Stockert 1998, Jäger, 2000]. Based on these data, a pilot study in patients with metastatic STS evaluated the activity of a dendritic cell based NY-ESO-1 vaccine as 2L or 3L therapy, wherein biomarker analysis revealed incremental T cell responses against NY-ESO-1 peptides in vaccinated patients, which correlated with improved survival [Pollack, 2017]. This vaccine was subsequently evaluated in a recent phase 3 trial in previously untreated (1L) NY-ESO-1^{+} metastatic STS and HLA-A*02:01^{+} patients, wherein patients completed anthracycline based chemotherapy and were then randomized to either receive the NY-ESO-1 vaccine as maintenance or placebo [NCT03520959]. This study was terminated early due to lack of clinical benefit.

Nevertheless, these data are indicative of the potential for these tumors to respond to immunotherapy, and of the relevance of NY-ESO-1 targeting. Indeed, adoptive transfer of lete-cel has demonstrated clinical responses in patients with metastatic synovial sarcoma who have failed prior treatment with standard chemotherapy and pazopanib (study 208466) and in patients with advanced myxoid/round cell liposarcoma (study 208469). The efficacy and safety of lete-cel in study 208466 and 208469 is described in the Lete-cel Investigator's Brochure and summarized in the Benefit/Risk section below.

In previous studies with lete-cel (see Section 3.2.2 below), objective responses have been observed with a response rate of 50%, a durability of response of 30.9 weeks, and median survival of approximately 24 months which represents a marked improvement over a median survival of 12 months in relapsed metastatic synovial sarcoma with current standard of care treatments. It is expected that treatment in first line setting for synovial sarcoma and myxoid/round cell liposarcoma should have similar outcomes.

In the frontline setting, adoptive immunotherapy with lete-cel may also facilitate a favorable alteration of the tumor immune microenvironment, that may further enhance activity of subsequent chemotherapy in this disease and the activity of other immunomodulating agents; thereby providing a mechanism for life extending treatment options to these patients.

These and other results (See Section 3.2.2 of this Substudy) demonstrating encouraging clinical activity of lete-cel across multiple NY-ESO-1 expressing tumor types, provide a reasonable rationale for testing lete-cel in a small pilot study for previously untreated patient population with advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, expressing NY-ESO-1.

3.2 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks as well as reasonably expected adverse events of lete-cel (GSK3377794) may be found in the Lete-cel Investigator's Brochure. It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation as these studies are designed to provide information about the safety and effectiveness of investigational medicines. This section outlines the potential benefits, risks and the mitigation strategy for this study.

3.2.1 Risk Assessment

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Lymphodepleting Chemotherapy (Fludarabine/Cyclophosphamide)		
• Myelosuppression • Immunosuppression • Bone Marrow Failure and Infection • Cardiotoxicity • Pulmonary Toxicity • Urinary Tract and Renal toxicity • Veno-occlusive disease • Secondary Malignancy • Hyponatraemia • Neurotoxicity	Cases were reported with both drugs.	Please refer to the prescribing information of fludarabine and cyclophosphamide and Section 12.7.
• Autoimmune haemolytic anaemia • Autoimmune thrombocytopenia • Decreased vision • Peripheral neuropathy	Cases were reported with fludarabine	Please refer to the prescribing information of fludarabine.
Lete-cel (GSK3377794)		
Cardiac arrest	Potential risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been 2 reports of unexpected fatal cardiac arrest. The first occurred 5 months after T-cell infusion and was confounded by hypotension due to poor oral intake and concurrent renal insufficiency. The second occurred approximately 1 week after T-cell infusion in the setting of a recent fungal catheter line infection, concurrent treatment with caspofungin and multifocal pneumonia / edema seen on chest CT	Participants with significant cardiac risk factors or with CRS $\geqslant$ Grade 2 will receive close cardiac monitoring (Core Section 9.3.6 and Section 12.7.5). Participants with lung metastases should be considered for pulmonary consultation prior to lymphodepletion ; participants deemed at high risk of pulmonary complications should be monitored closely (Core Section 9.3.7). Central lines should be closely monitored for infection (Core Section 12.7.2). Systemic fungal infections are excluded (Substudy 1 Exclusion 10) Monitoring of risk of increased cardiac toxicity with the use of anti-microbials (Core Section 12.7.2.6)
Cytokine release syndrome (CRS)	Identified risk due to TCR T-cell infusion considered adverse event of special interest (AESI)	Participants with pre-existing autoimmune disorders are excluded (Section 6.2 of this Substudy). Management for

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
		CRS is described in Section 12.7.5. Events Grade ≥3 must be reported as SAEs and submitted to GSK within 24 hours.
Graft versus host disease (GvHD)	Identified risk associated with TCR T cells reacting against normal tissues and organs considered an AESI	Participants with pre-existing autoimmune disorders are excluded (Section 6.2 of this Substudy). Management for GVHD is described in Section 12.7.6.
Haematopoietic cytopenias (including Pancytopenia with bone marrow failure/aplastic anemia)	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion, considered an AESI	Participants with cytopenias are excluded (Section 6.2 of this Substudy). Management for pancytopenia is described in Section 12.7.7.
Haemorrhage secondary to thrombocytopenia	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been reports of haemorrhage (including intracranial and pulmonary) in participants with severe prolonged thrombocytopenia.	Protocol guidance on Blood product support provides recommendation on platelets levels to be maintained in the in-patient setting and the out-patient setting, as per Section 12.7.3.
Hypersensitivity	Identified risk due to TCR-T cell infusion. Hypersensitivity reactions (including anaphylaxis) may be due to the 5% (v/v) DMSO inTCR-T formulation.	Participants with history of allergic reactions to any agents used in the study are excluded. See Section 6.2 for details. Participants will be premedicated against potential infusion reactions with antihistamines on the day of TCR-T cell infusion. See Section 7.1.4 for details.
Reactivation of previous viral infections after prolonged leukopenia	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion	Participants who have received radiation to bone marrow that would predispose them to prolonged cytopenia after lymphodepletion (in the investigator's opinion) are excluded. See Section 6.2 for details. Lymphodepletion dose will be modified in participants with potentially reduced bone marrow reserve. See Section 7.1.3 for details. Participants with active infection are excluded. Participants with CMV seropositivity will be monitored regularly for viral reactivation. For HSV/VZV prophylaxis, participants will receive acyclovir or valacyclovir for one year from LD. Prophylaxis will be given to those with

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
		HBV seropositivity. See Section 6.2 and Core Section 12.7.2 for details.
Neutropenia (including fatal neutropenia)	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion	Patients are excluded based on absolute neutrophil counts (Section 6.1.2). Investigator must discuss with Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in participants at risk (Section 7.1.3). G-CSF to be administered in accordance with ASCO guidelines or institutional practice (Section 7.1.3). Dose modifications are included for fludarabine and cyclophosphamide (Section 7.1.3) Grade 4 Neutropenia events lasting ≥28 days must be submitted to GSK within 24 hours (Core Section 9.4.7).
Decreased Vision	Potential risk: There was a report of decreased vision in a patient who received lete-cel infusion following lymphodepletion with fludarabine and cyclophosphamide.	Dose reductions for fludarabine for renal impairment are included (Section 7.1.3). Investigator must discuss with Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in patients at risk (Section 7.1.3)
Guillain-Barré syndrome (GBS) / Acute inflammatory demyelinating polyneuropathy	Potential risk associated with TCR T-cell infusion. Two participants who received lete-cel developed GBS.	Participants with prior or active demyelinating disease will be excluded (Section 6.2 of this Substudy). Neurologic consultation is required for participants with Grade 2 or higher neurologic events of a ≥7 day duration. Any potential future recurrence of GBS will lead to a pause in study enrollment until further investigation.
Treatment-related inflammatory response at tumor site(s)	Identified risk associated with TCR T-cell infusion	Routine monitoring and testing as clinically required.
Immune effector cell-associated neurotoxicity syndrome (ICANS)	Potential risk associated with inflammation in the brain following TCR-T infusion. There have been reports of ICANS in participants who received lete-cel.	Participants with brain metastases with features associated with increased risk of ICANS are excluded (Section 6.2 of this Substudy). Monitoring criteria for ICANS are described in Section 12.7.8.
Insertional oncogenesis	Potential risk in T cells transduced with lentiviral vector	Routine PV. To be monitored in the LTFU Protocol (208750) or LTFU portion of this study. Monitoring to

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
		follow the recommendations set forth in the FDA guidance, 2020a. PBMC samples are used as a surrogate sample for monitoring insertional oncogenesis by polymerase chain reaction (PCR) for gene modified cells in the blood.
Replication competent lentivirus (RCL)	Potential risk associated with use of lentivirus	Routine PV. To be monitored in the LTFU Protocol. Samples will be tested for the presence of VSV-G DNA copies (Section 9.3.11 in the Core Protocol).
On/Off-Target Off-Tumor Risks	Potential risk associated with use of TCR T-cell therapy	To be monitored in this protocol and in the LTFU Protocol. Protocol includes eligibility criteria (Section 6.1 and Section 6.2 of this Substudy), routine PV, and management strategies as appropriate to limit, diagnose, characterize and treat toxicities related to potential risks (Section 12.7).
Study Procedures		
Tumor biopsy	Bleeding, pain, swelling associated with the procedure	Biopsies are performed by trained personnel; image-guided when necessary and performed only if deemed safe.
Leukapheresis	Electrolyte imbalance and bleeding at the site of phlebotomy	Refer to local site procedures and guidelines.
Non Standard of Care Treatment in Frontline		
Delayed frontline chemotherapy	Potential risk that participant will not respond to lete-cel and will have delayed start of frontline chemotherapy	While participants are deferring standard of care chemotherapy, the protocol does allow for administration of 2 cycles of doxorubicin as bridging therapy prior to infusion with lete-cel. Time from end of bridging chemotherapy until the start of lymphodepletion is estimated to be approximately 3 weeks (due to washout). Participants will be monitored thereafter closely for progression / lack of response to lete-cel and will be treated subsequently at investigator discretion. Only those participants expressing NY-ESO-1 are eligible and therefore only those participants who are most likely to benefit from lete-cel will be treated.

The goal of the risk management measures is to maximize the chance of therapeutic benefit while mitigating and better understanding the risks of treatment with lete-cel.

The known safety profile of lete-cel is based on 166 enrolled and 125 treated participants as of 27 January 2021 as decribed in the Lete-cel Investigator's Brochure. The most commonly reported treatment-emergent adverse events which occurred in ≥50% of participants following lete-cel infusion were leukopenia/WBC decreased (81%), neutropenia/neutrophil count decreased (80%), nausea (78%), anemia/RBC decreased (78%), thrombocytopenia/platelet count decreased (77%), fatigue (70%), pyrexia (66%), diarrhea (57%), and lymphopenia/lymphocyte count decreased (54%). The most common Grade 3 and 4 AEs which occurred in ≥20% of participants following lymphodepleting chemotherapy and lete-cel infusion were leukopenia/WBC decreased (78%), neutropenia/neutrophil count decreased (74%), thrombocytopenia/platelet count decreased (62%), anemia/RBC decreased (58%), lymphopenia/lymphocyte count decreased (52%), febrile neutropenia (36%), and hypophosphatemia (27%). These AEs are consistent with expected immediate adverse events after lymphodepletion chemotherapy.

Across all studies, 47 (38%) participants had SAEs considered by the Investigator to be related to study treatment. Treatment-related SAEs occurring in more than 2 subjects following lete-cel infusion were: cytokine release syndrome (CRS) (15%), pyrexia (6%), neutropenia/neutrophil count decreased (5%), rash/rash maculo-papular (4%), thrombocytopenia/platelet count decreased (4%) and febrile neutropenia (3%). For the 16 participants who received a second infusion, five treatment related SAEs were reported after second T-cell infusion, which included 1 (6%) case each of CRS, cytomegalovirus infection, embolism, febrile neutropenia, and rash/rash maculo-papular.

Among the adverse events of special interest,

1. CRS was reported in 52 (42%) cases (of 125) as of 27 January 2021 across all lete-cel clinical trials. Of these, there was 1 participant with Grade 4, 9 with Grade 3, 21 with Grade 2, and 19 with Grade 1. There were a total of 19 cases of CRS that were reported as SAEs. All 19 SAEs resolved in 2 weeks or less. Five of the 19 reported SAEs were treated with tocilizumab. Median duration of the CRS events was 8-9 days (range 1-28 days).
2. A total of 7 cases (of 125) of GvHD have been reported of which 3 cases were reported as an SAE. All cases were Grade 1-3, occurred in patients with multiple myeloma, and completely recovered with supportive treatment. Six (6) out of 7 participants with reported GvHD were from Study 209393 (formerly ADP-01411) which required an allogeneic stem cell transplant prior to the T-cell infusion.
3. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), originally named as 'encephalopathy' was reported in 1 case with multiple brain metastasis, that was transient, and resolved in 2 days with supportive care.
4. Five (5%) participants had reported treatment-emergent AE of pancytopenia (3 participants: 2 with Grade 3, and 1 with Grade 1) or bone marrow failure (2 participants: 1 with Grade 5 fatal, and 1 with Grade 2) (refer to Lete-cel Investigator's Brochure for details).

5. GBS has been reported in 2 participants, both of which completely recovered with standard gamma globulin treatment.

To date, none of the analyses for insertional oncogenesis and replication competent lentivirus have been positive.

Pediatric Participants

This substudy allows pediatric participants 10 years of age or older. Previously, 2 pediatric participants have been treated in Study 208466 (ADP-04511). The first was a 15-year-old caucasian hispanic female treated in Cohort 3 of the study in which a milder, cyclophosphamide-only containing lymphodepletion regimen was used prior to T-cell infusion; and this participant achieved PR after the first infusion, progressed 9 months following treatment, and received a second infusion and achieved stable disease, and she died in September 2018, nearly 2 years after initial treatment with GSK3377793. The second participant was a 12-year-old caucasian female enrolled into Cohort 2; which included participants with tumors that have low NY-ESO-1 expression levels and received a high dose cyclophosphamide and fludarabine containing lymohodepletion regimen prior to lete-cel infusion. This participant achieved SD as her best response, subsequently progressed 8 months following lete-cel treatment, and died 11 months after lete-cel treatment.

As of 24 February 2019, a total of 29 AEs were reported for both pediatric participants as definitely or probably related to lete-cel. A total of 14 Grade 4 AEs (5%) were reported, none of which were reported as being related to lete-cel. The first participant experienced 2 SAEs: acute cholecystitis and CMV infection. Neither event was reported as related to study drug, and both events resolved. There were no SAEs reported by the second participant. There were 5 events of cytokine release syndrome reported. All events were Grade 1 or 2, and all resolved. Overall, the observed AEs are similar to those observed in adult participants treated with lete-cel, with the vast majority consistent with events observed as a result of the lymphodepletion regimen.

3.2.2 Benefit Assessment

As of 27 January 2021, 125 participants have been treated with lete-cel. Objective responses have been observed in the ongoing synovial sarcoma study (208466/ADP-04511) and in multiple myeloma post-autologous transplant study (209393/ADP-01411) [Lete-cel Investigator's Brochure].

In Cohort 1 of study 208466 (which is similar to the treatment regimen proposed for this protocol), a single infusion of lete-cel demonstrated an encouraging response rate of 50% (6/12 participants, 95% CI: 0.21-0.79), with an encouraging durability of response of 30.9 weeks (95% CI: 14-72) and one participant demonstrating a complete response. Importantly, the responses induced after T-cell infusion were associated with a median survival of approximately 24 months, which represents a marked improvement over a median survival of 12 months in relapsed metastatic synovial sarcoma.

Objective responses have been observed in 21 (84%) out of 25 of participants in multiple myeloma after autologous transplant (study 209393/ADP-01411) [Lete-cel Investigator's Brochure].

Additionally, 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 synovial sarcoma. The estimated overall three and five-year survival rates for these patients with synovial sarcoma were 38% and 14%, respectively [Robbins, 2015].

More recently, responses have also been observed in patients with myxoid round cell liposarcoma (MRCLS , study 208469) [D'Angelo, 2018a], thereby demonstrating encouraging clinical activity of lete-cel across multiple NY-ESO-1 and LAGE-1a expressing tumor types.

3.2.3 Overall Benefit/Risk Conclusion

Treatment with letetresgene autoleucel (lete-cel, GSK3377794) has been well tolerated in 103 participants with different tumor types [Lete-cel Investigator's Brochure]. Toxicities associated with engineered T-cell infusion, specifically CRS, have been observed in less than one third of the treated participants, were of low grade, and managed with supportive care in the majority of cases. To date, lete-cel has demonstrated an AE profile that has generally been manageable and acceptable in the context of benefit/risk assessment.

As described in this section, other agents, including frontline agents, have failed to demonstrate survival benefit or improvement in response rates over approved standard chemotherapy. In pilot studies, treatment with lete-cel has demonstrated objective responses in participants with relapsed metastatic disease that were durable and that extended survival in treated participants, therefore representing a meaningful clinical benefit and a marked improvement over current standard of care treatments in relapsed metastatic synovial sarcoma and myxoid/round cell liposarcoma. It is expected that treatment in first line setting should have similar outcomes. In the frontline setting, adoptive immunotherapy with lete-cel may also facilitate a favorable alteration of the tumor immune microenvironment, which may further enhance activity of subsequent chemotherapy in this disease, and the activity of other immunomodulating agents; thereby providing a mechanism for life extending treatment options to these participants.

This substudy is enrolling a previously untreated participant population for whom an approved standard of care exists. While there is a potential risk that participants will not respond to lete-cel and will have delayed start of frontline chemotherapy, participants can receive 2 cycles of approved standard chemotherapy (doxorubicin) while awaiting lymphodepleting chemotherapy and the time from end of bridging chemotherapy to start of lymphodepletion is estimated to be approximately 3 weeks (due to washout). Participants will be monitored thereafter closely for progression / lack of response to lete-cel and will be treated subsequently at investigator discretion.

In view of the clinical responses observed in relapsed, refractory participants, and results demonstrating encouraging clinical activity of lete-cel across multiple NY-ESO-1 expressing tumor types, and as per the risk assesment presented above, the benefit/risk ratio provides a reasonable rationale and acceptable risk for testing lete-cel in NY-ESO-1-positive synovial sarcoma and myxoid/round cell liposarcoma in this small pilot study for previously untreated participant population.

4 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of lete-cel in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 positive advanced synovial sarcoma or myxoid/round cell liposarcoma	Overall Response Rate (ORR) per RECIST v1.1 assessed by Investigators
Secondary - Efficacy	
To further evaluate the efficacy of lete-cel in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 positive advanced synovial sarcoma or myxoid/round cell liposarcoma	• Time to Response (TTR) • Duration of Response (DoR) • Disease Control Rate (DCR) • Progression Free Survival (PFS)
Secondary - Safety	
To evaluate the safety and tolerability of lete-cel in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 positive advanced synovial sarcoma or myxoid/round cell liposarcoma	• Frequency and severity of Adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in protocol) • Replication Competent Lentivirus (RCL) • Instances of Insertional oncogenesis (IO)
Secondary - Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 specific (c259) T cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit
Exploratory / Other	
CCI [redacted]	

Objectives	Endpoints
CCI	

AE/s = adverse event/s; AESI/s: adverse event/s of special interest; AUC (0-t) = area under the time curve from zero to time t; Cmax = maximum concentration; DOR = duration of response; HLA = human leukocyte antigen; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; Tmax = Time to Cmax; TTR = Time to Response

5 SUBSTUDY DESIGN

5.1 Overall Design

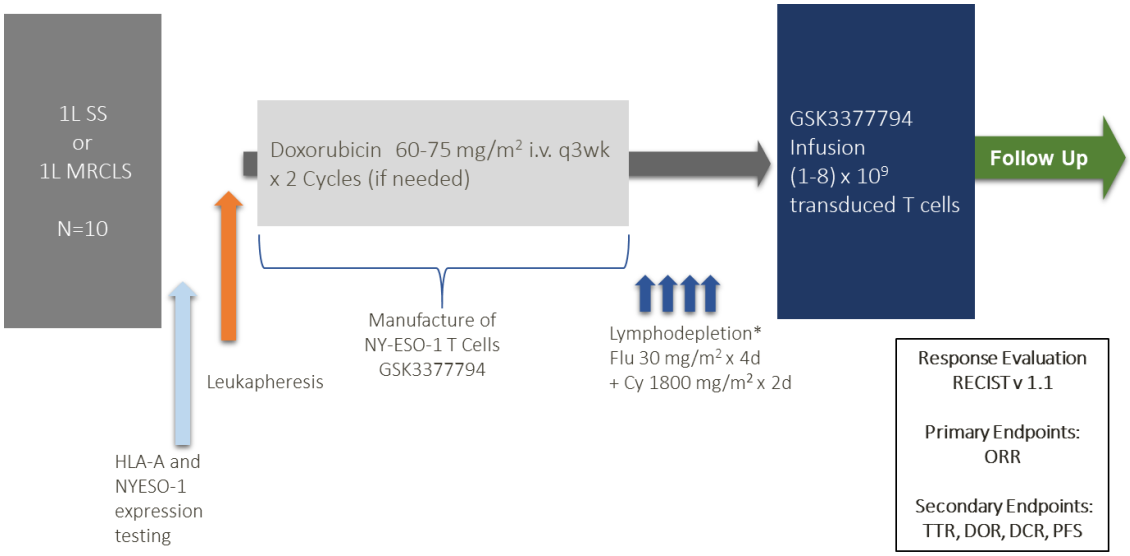
Study 208467 Substudy 1 is a multicenter, open-label study evaluation of the safety and efficacy of letetresgene autoleucel (lete-cel, GSK3377794) in participants with synovial sarcoma or myxoid/round cell liposarcoma.

For evaluation of lete-cel in synovial sarcoma and myxoid/round cell liposarcoma, this Substudy will enroll 10 previously untreated participants with advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma (Figure 1).

Participants identified by the Investigator as possible candidates for the study must have completed target expression screening for HLA-typing and NY- ESO-1 antigen expression; participants with the HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 alleles and whose tumor expresses the NY-ESO-1 antigen above the cut-off according to the applied immunohistochemistry assay are eligible to undergo further screening for this study.

This substudy will start with the clinical drug product supply and may use intended commercial drug product supply once it is available and the regulatory document has been amended to support this supply. Drug product supply type ('clinical' vs 'commercial') will be recorded in the CRF as part of the route of synthesis.

Figure 1 Substudy 1 Design



* The lymphodepleting regimen is to be adjusted as described in Section 7.1.3 of this Substudy.

Participants will undergo stepwise enrollment on the study followed by treatment according to defined phases within this substudy (See Figure 2 Participant Journey Schema below) which will include:

Part 1: Screening

1) Target expression screening for the presence of HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 type and tumor expression of NY ESO-1,

   (Note: If a participant was previously tested for HLA and/or NY-ESO-1/LAGE-1a expression under a different GSK-sponsored protocol, testing of HLA and/or NY-ESO-1 for 208467 may not be required dependent on the test platform(s) used and whether they meet the 208467 protocol requirements [see Section 6.3 of the Core Protocol])

2) Leukapheresis screening phase to determine eligibility for undergoing leukapheresis beginning up to 28 days prior to the day of 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,

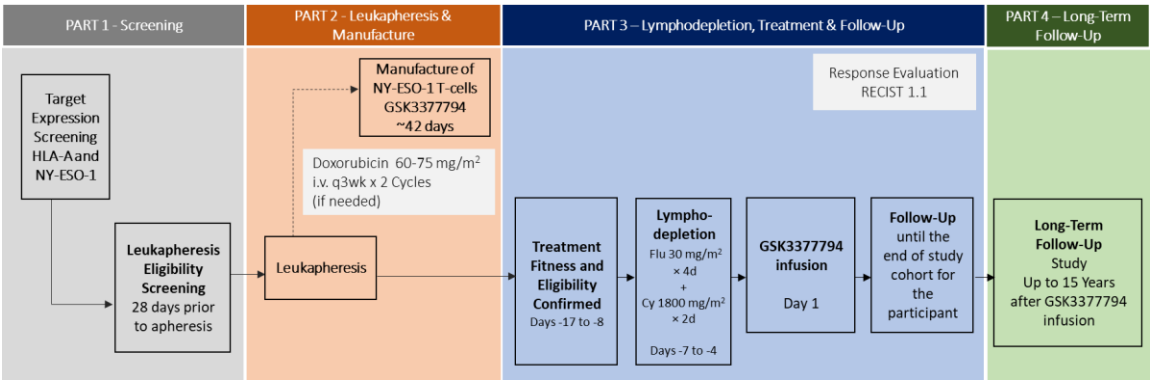
5) Interventional phase including Lymphodepletion from Days -7 to -4, lete-cel infusion on Day 1 and follow-up until the end of study (as defined in Section 5.3 of this Substudy),

   (Note: TCR engineered T-cell 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 lete-cel infusion.

Figure 2 Participant Journey Schema



* The lymphodepleting regimen is to be adjusted as described in Section 7.1.3 of this Substudy.

Part 1: Screening

See Core Protocol Section 5 of this Substudy for complete details of screening approach. Inclusion / exclusion criteria are listed in Section 6.

This substudy will enroll previously untreated (first line) participants with advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.

Participant screening may start at any time after diagnosis of high-risk locally advanced (i.e. deeply seated, high grade, positive margins, large [≥5 cm], or locally recurrent) synovial sarcoma or myxoid/round cell liposarcoma disease.

Disease progression may be present but is not mandatory for screening. Screening will consist of two phases: target expression screening and leukapheresis eligibility screening.

For target expression 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 expression will also be evaluated on tumor tissue from a formalin-fixed and paraffin-embedded (FFPE) archival (most recent preferred) or fresh biopsy (see Tumor biopsies section below for more details). 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.

Note: target expression Screening may also be performed under a separate Screening protocol such as athe GSK molecular disease characterization initiative (MDCI) study (213299), or under other NY-ESO-1/LAGE-1a T-cell protocols.

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

Part 2: Leukapheresis/Manufacture

In this first line population, participants may receive up to 2 cycles of doxorubicin between leukapheresis and lymphodepletion as outlined in Section 7.1.2 of this Substudy.

The initiation of leukapheresis procedure constitutes enrollment in the study. The collected T cells will be sent for manufacturing.

See Core Protocol Section 5 for complete details of leukapheresis and manufacture approach.

Part 3: Lymphodepletion/Treatment

See Core Protocol Section 5 for complete details of lymphodepletion and treatment approach.

Part 4: LTFU

See Core Protocol Section 5 for complete details of the long term follow up study. See end of substudy definition in Section 5.3 of this Substudy for details of participant transition to LTFU.

Tumor Biopsies

Archival tumor FFPE or fresh biopsy from a representative tissue is required from all participants to be used for antigen expression (NY-ESO-1) eligibility screening. If multiple archival samples are available, then the most recent archival sample should be used. If fresh biopsy is performed, then this tissue should be used:

a. Formalin-fixed paraffin embedded (FFPE) tumor specimens in paraffin blocks are preferred. A minimum of 20 unstained slides (5-micron serial fresh cut) is required as an alternative. Patients with fewer than 20 unstained slides may still be considered for screening following discussion with Medical Monitor
b. Acceptable specimens include core needle biopsies from deep tumor tissue (minimum 3-5 cores x 18G or larger and approximately 1 cm long) or excisional, incisional punch or forceps biopsies for cutaneous, subcutaneous or mucosal lesions
c. Fine-needle aspiration, brushing, cell pellet from pelural effusion, bone metastases, and lavages are not acceptable
d. Tissue should be obtained from 1 year of consent and be of good quality on the basis of total and viable tumor unless discussed with Medical Monitor

A pre-treatment tumor sample collected within 90 days prior to initiating lymphodepletion is required for Substudy 1. This biopsy will be used as baseline for biomarker analyses. If it is not feasible to obtain a fresh biopsy, an archival tumor biopsy (FFPE block) preferably taken 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 bridging or standard of care intermediate anti-cancer therapy, the screening biopsy will be used for baseline.

Additional biopsies will also be collected at Week 4, and at disease progression. In exceptional cases, where such biopsies cannot be collected, these may be deferred in consultation with the sponsor. These cases include participants for whom there is no safely accessible tumor tissue; or if conducting such a biopsy would compromise the medical condition of the participant; or if other clinical considerations preclude conduct of the biopsy procedure. In addition to the indicated collection times, tumor biopsies can be obtained at any time during the study execution.

See Core Protocol Section 9.9.1 for other biopsy considerations.

5.2 Number of Participants

It is anticipated that Substudy 1 will enroll 10 participants with previously untreated advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, that is either newly diagnosed or relapsed after surgery and radiotherapy and /or adjuvant therapy.

5.3 End of Study Definition

5.3.1 End of Substudy for Individual Participants

a) End of **Interventional phase** for individual participants

A participant is considered to have completed the Interventional phase of the Substudy when one of the following occurs (whichever is sooner):

- Participant has confirmed disease progression (also need to ensure that participant is followed for SAEs through 90 days following T-cell infusion, or 30 days following T-cell infusion if the participant initiates new anticancer therapy, whichever is earlier);
- Participant dies;
- Interventional phase ends for the Substudy (See Section 5.3.2 of this Substudy).

If participant withdraws consent or is withdrawn for other reasons prior to end of their Interventional phase, they will be considered early withdrawal.

All participants alive after confirmed disease progression will be followed in a separate long term follow up (LTFU) protocol (GSK study 208750) for observation of delayed AEs and survival for a duration of 15 years post-T-cell infusion in accordance with FDA [FDA, 2020a] and EMA guidance [EMA, 2009]. If LTFU protocol is not yet available at the particular clinical site, participants may be temporarily followed per LTFU schedule under this protocol (Section 2 Table 5 of this Substudy) until LTFU protocol becomes available. The transfer of any individual participant to the LTFU protocol 208750 should not exceed 6 months.

b) End of **Substudy** for individual participants

The substudy ends for an enrolled participant when they have transferred to the separate LTFU protocol (GSK study 208750), declined consenting to the separate LTFU protocol, completed LTFU requirement in this study, have been lost to follow-up, or withdrawn, or died.

5.3.2 End of Substudy

a) End of **Interventional** phase:

The interventional phase ends when all enrolled participants have withdrawn early or have been dosed and confirmed disease progression, died or have been lost to follow-up.

All participants alive after the end of the Interventional Phase of the substudy, will be followed in a separate long term follow up (LTFU) protocol (GSK study 208750) for observation of delayed AEs and survival for a duration of 15 years post-T-cell infusion in accordance with FDA [FDA, 2020a] and EMA guidance [EMA, 2009]. If LTFU protocol is not yet available at the particular clinical site, participants may be temporarily followed per LTFU schedule under this protocol (Section 2 of this Substudy) until LTFU protocol becomes available. The transfer of any individual participant to the LTFU protocol 208750 should not exceed 6 months.

b) End of **Substudy**:

The substudy ends when all treated participants have transferred to the separate LTFU protocol (GSK study 208750), declined consenting to the LTFU protocol, completed LTFU requirement in this study, have been lost to follow-up, or withdrawn early, or died.

5.4 Scientific Rationale for Substudy Design

There is lack of effective treatments for metastatic synovial sarcoma and myxoid/round cell liposarcoma. The currently approved chemotherapy regimens provide limited durability of clinical efficacy with response rates in 18-28% range lasting 4-6 months in STS. NY-ESO-1 (c259) specific T cells (lete-cel, GSK3377794) have demonstrated response rates of ~50% in 2L+ metastatic synovial sarcoma with survival benefit. To improve survival and treatment options for participants, in this substudy we will explore the efficacy, including survival benefit, and safety as well as feasibility of this treatment in participants with newly diagnosed advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma disease.

5.5 Justification for Dose

5.5.1 Justification of Lymphodepleting Regimen

Based on prior experience with lete-cel in participants with synovial sarcoma and melanoma, where similar lymphodepletion regimen was associated with optimal responses [Merchant, 2015; D'Angelo, 2018b], the lymphodepleting regimen for participants treated under protocol amendments 1-5 has been to administer fludarabine, 30 mg/m^2/day × 4 days (Day -7 to -4) and cyclophosphamide, 1800 mg/m^2/day × 2 days (Day -5 to -4), with lete-cel infusion on Day 1.

Based on additional safety data (prolonged neutropenia; fatal neutropenia [see IB, GlaxoSmithKline Document Number RPS-CLIN-015027, 2021]) and modelling data, to further optimize lymphodeletion and reduce potential for acute and prolonged cytopenias while also minimizing impact on efficacy, the cyclophosphamide cumulative dose is modified from 3600 to 2700 mg/m^2. The fludarabine dose remains unchanged.

This regimen was previously used in Study 208469 (Cohort 2) in MRCLS, and the dosing is currently in use for NSCLC participants in Study 208471 (slightly different schedule).

The refined lymphodepleting regimen for participants treated as of protocol amendment 6 is as follows:

- Fludarabine, 30 mg/m^2/day × 4 days (Day -7 to -4) and
  Cyclophosphamide, 900 mg/m^2/day × 3 days (Day-6 to -4),
  with lete-cel infusion on Day 1.

Rules for further dose reductions on cyclophosphamide are also adapted by applying the same 33% reduction as previously used (in protocol amendments 1-5) as follows:

- As of protocol amendment 6, a standard reduction for cyclophosphamide dose (in mg/m^2) of 2700 = 900 × 3 days is to use 1800 = 600 × 3 days.

5.5.2 Justification of lete-cel (GSK3377794) Dose

A dose range of 1×10^9 to 8×10^9 total transduced T cells had initially been chosen as it was within the cell dose in which clinical responses were observed without significant toxicity in previous clinical trials and which was logistically feasible to manufacture (based on initial assumptions related to yield).

At this target dose, lete-cel has resulted in objective responses in participants with metastatic synovial sarcoma, metastatic melanoma [Robbins, 2015], and multiple myeloma [Rapoport, 2015] whose tumors expressed the NY-ESO-1 or LAGE-1a antigens and who met the HLA inclusion criteria.

This cell dose range was included in protocol amendments 1 through 5.

Optimization of the dose range:

A cell dose of 15×10^9 transduced T cells represents the updated upper end of what is logistically deemed feasible to manufacture.

As such, the upper end of the target dose range of transduced T cells is increased from 8×10^9 to 15×10^9 in order to maximize the delivery of cells for participants whose manufacture yields $>8 \times 10^9$ transduced T cells.

Patients have previously been treated at this upper end of the revised dose range: in two older pilot studies (synovial sarcoma Study 208466 and multiple myeloma Study 209393), 3 patients received doses $>8 \times 10^9$ (up to 14.4×10^9) transduced T cells with no safety signals identified.

Other TCR T cells have been reported safe at even higher doses: the genetically engineered T cells with a TCR targeting human papilloma virus-associated epithelial cancer HPV-16 E7 (E7 TCR) were reported in a first-in-human, phase 1 clinical trial of 12 participants, to not show any dose limited by toxicity with a maximum dose of 100×10^9 engineered T cells administered [Nagarsheth, 2021].

Since no dose-toxicity relationship has been established todate on 125 patients dosed with lete-cel (see Lete-cel Investigator's Brochure), it is anticipated that the safety profile in patients who receive doses up to the theoretical 15×10^9 transduced cells will remain comparable to the current safety profile.

- For participants treated as of protocol amendments 6, any released manufactured product counting between (1-15) $\times 10^9$ transduced cells will be shipped in its entirety for infusion as a single dose.

Due to the sample size and tight control over product release, participants receiving doses $>8 \times 10^9$ will be closely monitored with ongoing review by the SRT.

6 STUDY POPULATION

Inclusion/Exclusion criteria *are grouped into 3 parts and eligibility screening will take place in the following 3 steps:*

- ***Target expression screening:*** *A set of criteria permitting participants' blood to be screened for HLA-type and an archival or fresh tumor sample to be screened for the expression of NY-ESO-1.*
- ***Leukapheresis eligibility screening:*** *To be fulfilled prior to performing leukapheresis procedure.*
- ***Treatment eligibility screening:*** *To be fulfilled prior to starting lymphodepletion procedure.*
  - ***Treatment fitness (for safety):*** *To be evaluated prior to commencing lymphodepleting chemotherapy and administration of lete-cel (GSK3377794).*

6.1 INCLUSION CRITERIA

6.1.1 *Target Expression Screening*

*Participants are eligible to be screened for target expression (HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1) only if all of the following criteria apply:*

1. Capable of giving signed informed consent including compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol. For participants <18 years of age (or the legal minimum age in the relevant country) their legal guardian must give informed consent. Pediatric participants will be included in age-appropriate discussion in order to obtain assent.
2. Participant must be ≥10 years of age at the time of signing the informed consent. Participant scheduled to receive *clinical* drug product supply must also weigh ≥40 kg. For participant scheduled to receive intended *commercial* drug product supply and weighing <40kg, the Investigator must also consult with the Medical Monitor prior to inclusion.
3. Participant has a diagnosis of synovial sarcoma or myxoid/round cell liposarcoma, confirmed by local histopathology with evidence of disease-specific translocation.

   Note: Evidence of a relevant disease-specific translocation is required at latest prior to leukapheresis (Inclusion 9).
4. Participant has at minimum high-risk locally advanced (i.e. deeply seated, high grade, positive margins, large [≥5 cm], or locally recurrent) or advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.
5. Participant with synovial sarcoma or myxoid/round cell liposarcoma who is
   a) Newly diagnosed, previously untreated OR
   b) Relapsed after surgery or radiotherapy for localized disease OR
   c) Relapsed ≥1 year after adjuvant/neoadjuvant therapy for localized disease

6. Male or female. Contraception requirements will apply at the time of leukapharesis and treatment.
7. 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 a recent NY-ESO-1 expression test result from the same designated central laboratory, following the same procedures, has already been performed under a separate GSK-sponsored protocol or under another substudy. For guidance on acceptable specimen material see Tumor Biopsies under Section 5.1.

6.1.2 *Leukapheresis Eligibility Screening*

Prior to finalizing participant treatment plan, please note that bridging/standard of care anti-cancer therapy is allowed under Section 7.1.2 conditions but that there are washout requirements prior to leukapheresis and prior to lymphodepletion. Additional considerations should be given to accumulated radiotherapy prior to lymphodepletion. All the Inclusion Criteria from Section 6.1.1 must apply again prior to leukapheresis. In addition, the following criteria must also apply:

8. Life expectancy ≥24 weeks
9. Participant has confirmed evidence of a relevant disease-specific translocation per below:
    - For *synovial sarcoma*, presence of a translocation involving chromosome 18 (SYT gene) and/or chromosome X (SSX1, SSX2 or SSX4 genes);
    - For *myxoid/round cell liposarcoma*, presence of a translocation involving chromosome 12 (DDIT3 gene) and/or chromosome 16 (FUS gene) and/or chromosome 22 (EWSR1 gene).

    Note: Methods, such as, but not limited to, fluorescence in situ hybridization (FISH) assay or Next Generation Sequencing (NGS) or Immuno HistoChemistry (IHC) using fusion-specific antibody are commonly used to detect translocations.
10. Participant has advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma. Unresectable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise.
11. Participant must be positive for HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles by a validated test in a designated central lab prior to leukapheresis.

    NOTE: If a participant was previously tested for HLA type under a different GSK-sponsored protocol, testing of HLA type for 208467 may not be required dependent on the test platform(s) used and whether they meet the 208467 protocol requirements [see Section 6.3 of the Core Protocol].
12. Participant's tumor has been pathologically reviewed by a designated central laboratory with confirmed positive NY-ESO-1 expression defined as ≥30% of cells that are 2+ or 3+ by immunohistochemistry.

    NOTE: If a participant was previously tested for NY-ESO-1 expression under a different GSK-sponsored protocol, testing of NY-ESO-1 expression for 208467 may not be required dependent

on the test platform(s) used and whether they meet the 208467 protocol requirements [see Section 6.3 of the Core Protocol].

13. Left ventricular ejection fraction ≥45% with no evidence of clinically significant pericardial effusion.
14. Performance status: for participants <16 years of age, Lansky >60, or for participants ≥16 and <18 years of age, Karnofsky >60, or for participants ≥18 years of age, Eastern Cooperative Oncology Group (ECOG) of 0-1.
15. Participant must have adequate organ function and blood cell counts, within 7 days prior to the day of leukapheresis procedure, as indicated by the following laboratory values in Table 5.

Table 5 Definitions of Adequate Organ Function

System	Laboratory Value
Hematological[a,b,c]	
Absolute Neutrophil count (ANC)	≥1.5 x10^9/L (without granulocute colony-stimulating support)
Absolute Lymphocyte count (ALC)	≥0.5 x 10^9/L
Hemoglobin	≥8 g/dL or ≥5.0 mmol/L (without transfusion support)
Platelets	≥100 x10^9/L (without transfusion support)
Renal	
Creatinine clearance ≥40 mL/min • Participants who are ≥18 and <65 years of age must be assessed either: ○ by 24-hour urine creatinine collection OR ○ by using Serum Creatinine (Scr) via an estimated creatinine clearance (CrCl) calculated as outlined below by using the CKD-EPI equation and adjusting the result by multiplying with (BSA/1.73) to obtain CrCl in mL/min: Step 1: estimated glomerular filtration rate (GFR) to be obtained from the Chronic kidney disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009]: **Estimated GFR** (mL/min/1.73m^2) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 *[if female]* × 1.159 *[if black]* *where*: Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min(Scr/κ,1) indicates the minimum of Scr/κ or 1, max(Scr/κ,1) indicates the maximum of Scr/κ or 1, and Age is in years. Step 2: correction factor to be applied per the American National Kidney Foundation in order to obtain the estimated creatine clearance in mL/min **Estimated CrCl** (mL/min) = **Estimated GFR** (mL/min/1.73 m^2) × **BSA (m^2) / 1.73** To calculate the BSA for fludarabine dosing, use actual body weight. An adjusted body weight (ABW) may be required for cyclophosphamide, see below for further details. • Participants ≥65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement, according to standard practice at the treating institution. • Participants <18 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement or by serum creatinine collection, according to standard practice at the treating institution.	

<table>
<tr><th>System</th><th>Laboratory Value</th></tr>
<tr><td colspan="2">Participants <18 years of age must have GFR≥ 70mL/min/1.73m^2 OR have a serum creatinine based on age/gender as follows:
<table>
<tr><th>Age</th><th colspan="2">Maximum serum creatinine (mg/dL)</th></tr>
<tr><th></th><th>Male</th><th>Female</th></tr>
<tr><td>10 to < 13 years</td><td colspan="2">1.2</td></tr>
<tr><td>13 to <16 years</td><td>1.5</td><td>1.4</td></tr>
<tr><td>16 to <18 years</td><td>1.7</td><td>1.4</td></tr>
</table></td></tr>
<tr><td colspan="2">Hepatic</td></tr>
<tr><td>Total bilirubin
Participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)</td><td>≤1.5 x ULN (isolated bilirubin ≤1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)</td></tr>
<tr><td>ALT</td><td>≤2.5 x ULN (or ≤5 x ULN if documented history of liver metastases)</td></tr>
<tr><td colspan="2">Coagulation[d]</td></tr>
<tr><td>International normalized ratio (INR) OR prothrombin time (PT) /
Activated partial thromboplastin time (aPTT)</td><td>≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants</td></tr>
<tr><td colspan="2">Nutritional status</td></tr>
<tr><td>Albumin</td><td>≥3.5 g/dL</td></tr>
</table>

a. No platelet transfusions within 14 days.
b. No red blood cell transfusions to meet minimum hematologic values for eligibility.
c. Organ function will be reassessed prior to **lymphodepletion**: if, upon consultation with the Medical Monitor, there is evidence from laboratory values that recovery from last anti-cancer treatment is underway, hematology labs may be considered acceptable and requirements waved to proceed with lymphodepletion.
d. Prior to **lymphodepletion**, please refer to Section 7.5.2 for guideline on use of anticoagulant medications.

16. Participant is fit for leukapheresis and has adequate venous access for the cell collection.
17. Male or female. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or until persistence of gene modified cells in the participant's blood is below the level of detection for 2 consecutive assessments, whichever is longer.

Refrain from donating sperm

Plus, either:

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

OR

- Must agree to use contraception/barrier as detailed below

- Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception described in Section 12.4 when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant (as a condom may break or leak)
- Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

b. Female Participants:

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

- Is not a WOCBP as defined in Section 12.4

OR

- Is a WOCBP (as defined in Section 12.4) who will agree to use a barrier method (male condom) and use a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Section 12.4 during the intervention period and 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. WOCBP should also agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before any dose of study intervention.

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

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

18. Female participants of childbearing potential (FCBP) must have a negative urine or serum pregnancy test.

6.1.3 *Treatment Eligibility Screening*

In addition to confirming Treatment fitness per Section 6.1.3.1, the following criteria must also apply prior to lymphodepletion:

19. Participant has measurable disease according to RECIST v1.1.
20. A biopsy (excisional, incisional, or core) of non-target tumor tissue obtained within 90 days prior to initiating lymphodepleting chemotherapy is mandatory if clinically feasible. This biopsy will be used as baseline for biomarker analyses. If it is not feasible to obtain a fresh biopsy, an archival tumor tissue (FFPE block) preferably

taken 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 bridging or standard of care intermediate anti-cancer therapy, the screening biopsy will be used for baseline.

21. A hematologist has been consulted prior to lymphodepletion in participants who have had a serious/significant bleeding/thrombosis history.

6.1.3.1 Treatment Fitness (for Safety)

Given potential changes in clinical status between screening/enrollment and the start of lymphodepleting chemotherapy, safety assessments from Section 6.1.1 and Section 6.1.2 will be reassessed prior to lymphodepletion. If the results of any assessments or procedure are outside of the eligibility criteria, please consult with the GSK Medical Monitor prior to proceeding with lymphodepletion.

6.2 EXCLUSION CRITERIA

6.2.1 *Target Expression Screening*

*Participants are not eligible to be screened for target expression (HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1) if any of the following criteria apply:*

1. Participant has been previously treated for advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.
2. Central nervous system (CNS) metastases.
3. Any other prior malignancy that is not in complete remission.

Exceptions include:

   a. completely resected non-melanoma skin cancer, or successfully treated *in situ* carcinoma (e.g. melanoma in situ, basal cell carcinoma, prostate cancer *in-situ*, periosteal osteosarcoma)
   b. previous malignancies that have been definitively treated, and have been in remission for 5 years may be enrolled upon consultation with sponsor Medical Monitor or designee

4. Previous treatment with genetically engineered NY-ESO-1 specific T cells.
5. Previous NY-ESO-1 vaccine or NY-ESO-1 targeting antibody.
6. Prior gene therapy using an integrating vector.
7. Previous allogeneic hematopoietic stem cell transplant.
8. Clinically significant systemic illness:

   c. Serious active infections or significant cardiac, pulmonary, hepatic or other organ dysfunction, that in the judgment of the Investigator would compromise the participant's ability to tolerate protocol therapy or significantly increase the risk of complications

   OR

d. Prior or active demyelinating disease

6.2.2 *Leukapheresis Eligibility Screening*

Participants are not eligible for leukapharesis if any of the Exclusion criteria from Section 6.2.1 apply. Please note in particular that mandatory washout period restrictions must be respected (Table 6) before starting leukapheresis. In addition, participants are not eligible for leukapharesis if any of the following criteria apply:

9. Participant has history of chronic or recurrent (within the last year prior to leukapheresis) severe autoimmune or immune mediated disease (e.g. Crohn's disease, systemic lupus) requiring steroids or other immunosuppressive treatments.
10. Uncontrolled intercurrent illness including, but not limited to:
    a. Ongoing or active infection (including, but not limited to systemic fungal infection)
    b. Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4
    c. Uncontrolled clinically significant arrhythmia
    d. Acute coronary syndrome (angina or myocardial infarction) in last 6 months
    e. Interstitial lung disease (participants with existing pneumonitis as a result of radiation are not excluded; however, participants cannot be oxygen dependent)
11. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per Investigator assessment).

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

12. QTc >480 msec

    NOTES:
    The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.

    The specific formula that will be used to determine eligibility for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

    For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

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

14. Pregnant or breastfeeding females (due to risk to fetus or newborn).
15. Prior/Concomitant Therapy:
    a. Any prior treatment-related toxicities must be CTCAE (Version 5.0) Grade ≤1 at the time of initiating study intervention (except for non-clinically significant toxicities e.g., alopecia, vitiligo). Participants with Grade 2 toxicities that are deemed stable or irreversible (e.g. chemotherapy related arthritis or tendinitis, skin discoloration or erythema) can be enrolled.
    b. Other standard of care lines of therapy are allowed only if guidelines and washout periods are followed as described in Table 6.
16. Investigational treatment within 30 days or 5 half-lives (whichever is shorter) prior to leukapheresis. Investigational vaccines (other than NY-ESO-1 vaccines that are not allowed) must follow the washout period specified in Table 6. Exceptions to this rule must be evaluated by the Investigator in agreement with the Sponsor's Medical Monitor (or designee).
17. Participant has active infection with HIV, HBV, HCV, EBV, CMV, syphilis, or HTLV as defined below:
    - Positive serology for HIV;
    - Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Participants who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation;
    - Active hepatitis C infection as demonstrated by hepatitis C RNA test. Participants who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative Screening RNA value;
    - Active EBV infection. Participants with positive EBV serology need to undergo additional tests/assessments in order to rule out active infection;
    - Active CMV infection. Participants with positive CMV serology need to undergo additional tests/assessments in order to rule out active infection;
    - Positive test for syphilis (spirochete bacterium);
    - Positive serology for HTLV 1 or 2.
18. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

6.2.3 *Treatment Eligibility Screening*

Please note that mandatory washout period restrictions must be respected (Table 6) before starting lymphodepletion. In addition to confirming Treatment fitness per Section 6.2.3.1, participants cannot proceed with lymphodepletion or treatment if any of the following criteria apply:

19. Participant has received cytotoxic therapy within 3 weeks prior to lymphodepleting chemotherapy.

20. Systemic corticosteroids or any other immunosuppressive therapy within 2 weeks prior to lymphodepleting chemotherapy.

    NOTE: Isolated doses of systemic corticosteroids are permitted to manage acute allergic reactions. Use of inhaled or topical steroids is not exclusionary

21. Participant has received ≥50 Gy to a significant volume of the pelvis, long bones or spine, or a cumulative dose of radiation that, in the Investigator's opinion would predispose patients to prolonged cytopenia after lymphodepletion.

22. All of the participant's measurable lesions have been irradiated within 3 months prior to lymphodepletion. An irradiated measurable lesion with unequivocal progression following irradiation may be considered a target lesion regardless of time from last radiotherapy dose.

    NOTE: There is no washout period for palliative radiation to non-target lesions

23. Participant has received an anti-cancer vaccine within 2 months in the absence of tumor response. The participant should be excluded if their disease is responding to an experimental vaccine given within 6 months.

24. Participant has received live vaccine within 4 weeks prior to lymphodepletion or intends to receive live vaccine during the 3 month period following administration of lete-cel.

25. Participant has received immune therapy (monoclonal antibody therapy, checkpoint inhibitors) within 4 weeks of lymphodepletion.

26. Participant had major surgery ≤28 days of first dose of study intervention.

Table 6 Washout Periods for Substudy 1

Treatment/Therapy[a]	Required Washout Prior to Leukapheresis	Required Washout Prior to Lymphodepletion[b]
Cytotoxic chemotherapy (including bridging chemotherapy)	3 weeks	
Live-virus vaccination (there is no required washout for seasonal flu vaccines that do not contain live virus).	4 weeks	
Systemic corticosteroids or any other immunosuppressive therapy (there is no washout required for inhaled or topical steroids as they are allowed during the study)	2 weeks	
Investigational treatment	4 weeks	2 weeks
Radiotherapy	To the target lesions within 3 months prior to lymphodepletion.[c] NOTE: There is no washout period for palliative radiation to non-target lesions	

a. Permission and washout for any other anticancer therapies must be discussed with the Sponsor's Medical Monitor (or designee).
b. Bridging therapy allowed on Substudy 1 between leukapheresis and lymphodepletion includes doxorubicin 60-75 mg/m^2 IV every 3 weeks for up to two cycles (see Section 7.1.2).
c. A lesion with unequivocal progression may be considered a target lesion regardless of time from last radiotherapy dose.

6.2.3.1 Treatment Fitness (for Safety)

Given potential changes in clinical status between screening/enrollment and the start of lymphodepleting chemotherapy, safety assessments from Section 6.2.1 and Section 6.2.2 will be reassessed prior to lymphodepletion. If the results of any assessments or procedure are outside of the eligibility criteria, please consult with the GSK Medical Monitor prior to proceeding with lymphodepletion.

6.3 Lifestyle Considerations

6.3.1 Meals and Dietary Restrictions

Participants should maintain the current/regular diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.3.2 Activity

Participants should abstain from extraordinarily strenuous athletic activity for 24 h before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

6.3.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. 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 lines of anti-cancer treatments and any serious adverse events (SAEs).

6.3.4 Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure or withdrawal) may be rescreened upon Sponsor agreement.
Rescreened participants will be assigned a new participant number.

For each rescreened participant, the Sponsor will review the following on evaluation of eligibility to Substudy 1 and before initiating leukapheresis or manufacturing of the T cells:

- Participant will be considered HLA positive if already tested positive for HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles by a validated test in a designated central lab under this substudy or under another GSK-sponsored study or substudy of this protocol;
- Participant's tumor antigen expression will be considered positive if previously pathologically reviewed by a designated central laboratory under this substudy or under another GSK-sponsored study or substudy of this protocol, with confirmed positive NY-ESO-1 expression defined as ≥30% of cells that are 2+ or 3+ by immunohistochemistry;

- If participant has previously completed Sponsor protocol-specified leukapheresis:
  - Already banked cryopreserved T cells under an applicable process may be used in the manufacturing of lete-cel if within shelf-life specifications;
  - Already stored manufactured lete-cel (GSK3377794) product under an applicable process may be used for the T-cell infusion if within shelf-life specifications.

7 STUDY INTERVENTION

7.1 Study Intervention(s) Administered

7.1.1 Leukapheresis

Participants will undergo leukapheresis to obtain starting material for the manufacture of autologous letetresgene autoleucel (lete-cel, GSK3377794).

Investigators will follow institutional guidelines and the minimum requirements as outlined in the Apheresis Manual.

A CD3 count of ≥200/µL prior to leukaheresis is recommended to ensure an adequate T-cell collection for manufacture of lete-cel. If the lab test returns a value lower than 200, there is the potential that more than one collection will be needed to reach the T-cell target. The lab test should be repeated, and the Sponsor alerted as soon as possible.

7.1.2 Bridging Therapy and/or Standard of Care Intermediate Anti-Cancer Therapy before Lymphodepletion

In this first line population, participants may receive doxorubicin 60-75 mg/m^2 IV every three weeks for up to two cycles between leukapheresis and the start of lymphodepletion. Use of doxorubicin is at Investigator's discretion in accordance with the label and local institutional guidelines. Clinically significant interactions have been reported for doxorubicin with inhibitors of CYP3A4, CYP2D6, and/or P-glycoprotein (P-gp) (e.g., verapamil) and also with inducers of CYP3A4 (e.g, phenobarbital, phenytoin, St. John's Wort), which may affect the concentration of doxorubicin, and therefore should be used with caution.

Mandatory washout periods (Table 6 Section 6.2 of this Substudy) must be respected. For therapies not already described in this protocol, washout periods must be around 5 half-lives, except for biologic agents for which a Sponsor consultation is required.

7.1.3 Lymphodepleting Chemotherapy

Prior to the administration of lymphodepleting chemotherapy, participant's fitness for lymphodepletion will be assessed, treatment eligibility criteria will be confirmed and baseline tumor assessment CT/MRI obtained per Section 9.1.1 of the Core Protocol and the SoA in this Substudy.

When lete-cel has been manufactured, has fulfilled release criteria, and is available for infusion at the site, lymphodepleting fludarabine and cyclophosphamide can be

administered as described in Table 7. Cyclophosphamide and fludarabine will be supplied by the pharmacy of the participating Institution.

Dose and regimen for lymphodepleting chemotherapy is adjusted for participants ≥60 years of age, as specified in Table 7. The investigator must discuss with the Sponsor's Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in situations such as but not limited to the following:

- Participants with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia),
- Participants with 3 or more prior lines of therapies,
- Participants with documented extensive prior radiation of the pelvis, long bones or spine,
- Participants with documented history of intensive chemotherapy that could reduce the bone marrow reserve,
- Participants with documented low albumin (≤3.5 g/dL).

A default dose adjustment for participants meeting one of the listed conditions above should be aligned to the standard dose modification otherwise applied for participants ≥60 years of age, as specified in Table 7.

For any conditions that are more complex, further discussion to determine the need for dose modification with the Sponsor's Medical Monitor or designee will be warranted.

For investigators with patients approaching lymphodepletion, Sponsor requires that site review creatinine clearance (CrCl) and lymphodepleting chemotherapy dose calculations with the Medical monitor or designee. Before lymphodepletion, site must provide Sponsor with intended doses (in mg/day) of fludarabine and cyclophosphamide, patient's height, weight, gender, ethnicity, baseline serum creatinine(s) and creatinine clearance (estimated or measured). Any significant discrepancy that would lead to a change in dose will be discussed with Medical monitor prior to commencing lymphodepletion.

- Calculations methods are provided in Section 6.1 Table 5 Definitions of Adequate Organ Function, Renal for CKD-EPI using BSA (e.g., DuBois), but institutions may use their own BSA calculator (e.g Mosteller), if required per local institutional practice.
- If there is variability in pre-leukapheresis and pre-lymphodepletion serum creatinine by ±30%, institution must consider more formal/accurate measure rather than rely on estimation of creatinine clearance.

If the infusion of lete-cel is delayed > 2 weeks, in general lymphodepleting chemotherapy should be repeated. The Investigator is expected to discuss the participant's condition and the treatment plan with the Medical Monitor.

Supportive therapy guidelines are provided in Section 12.7.

Table 7 Lymphodepleting Chemotherapy

	Lymphodepleting chemotherapy					Recommended prophylaxis and supportive medication
Day	**Drug**	**Dose, mg/m²**	**Dose for participants ≥ 60 years old, mg/m²**	**Route**	**Administration[c]**	Infection: On admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Section 12.7 or in line with institutional standard practice. Hydration: Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions Mesna: May be given to prevent urotoxicity per institutional guidelines or as recommended in this Section below. G-CSF: Must start ~24 hours after the last cyclophosphamide infusion (i.e., on Day -3). G-CSF support to continue until resolution of neutropenia in accordance with ASCO guidelines [Smith, 2015] or institutional practice.
-7	Fludarabine[1]	30	none	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	
-6	Fludarabine[1]	30	30	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	
	Cyclophosphamide[3]	900	600	IV	in 200 – 500 mL 0.9% NaCl over 1 hour[2]	
-5	Fludarabine[1]	30	30	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	
	Cyclophosphamide[3]	900	600	IV	in 200 – 500 mL 0.9% NaCl over 1 hour[2]	
-4	Fludarabine[1]	30	30	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	
	Cyclophosphamide[3]	900	600	IV	in 200 – 500 mL 0.9% NaCl over 1 hour[2]	
-3	Start G-CSF[4]					
+1	Lete-cel (GSK3377794)					

1. Fludarabine dose will be adjusted in renal impairment as described in this section. This adjustment needs to be applied to all doses, on top of the age-related modification. Fludarabine dose will not be adjusted by body weight per ASBMT guidelines that recommend dosing based upon body surface area (BSA) using actual body weight [Bubalo, 2014], unless required otherwise by institutional guidelines.
2. Or per institutional guidelines.
3. Cyclophosphamide dose will be adjusted in obese participants and in pediatric participants as described in this section. This adjustment needs to be applied to all doses, on top of the age-related modification.
4. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose ~24 hours after the last chemotherapy administered.

ASCO = American Society of Clinical Oncology; ASBMT = American Society for Blood and Marrow Transplantation practice; IV = intravenous; NaCl = sodium chloride; G-CSF = granulocyte-colony stimulating factor

Fludarabine Dose Adjustment for Renal Impairment

This adjustment needs to be applied to all doses, on top of the age-related modification. The dose of fludarabine will be adjusted for participants with renal dysfunction as follows:

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

Note: to estimate CrCl (in mL/min) please use Section 6.1 Table 5 for calculation steps before comparing to the thresholds given above.
If estimating CrCl using the CKD-EPI equation, adjust the result by multiplying by (BSA/1.73) to obtain a CrCl in mL/min. For fludarabine dosing for this BSA calculation, use actual body weight.
Creatinine clearance must be reassessed prior to lymphodepletion for use in these calculations.

Cyclophosphamide Dose Adjustments

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

Calculating Ideal Body Weight

	Estimated ideal body weight (IBW) in kg
Males	$\text{IBW} = (0.9 \times \text{height in cm}) - 88$
Females	$\text{IBW} = (0.9 \times \text{height in cm}) - 92$

Estimation of Ideal Body Weight may be performed per local institutional guidelines instead.

Calculating Adjusted Body Weight

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

$$\text{ABW} = \text{IBW} + 0.4 \times (\text{actual weight} - \text{IBW})$$

Estimation of Adujsted Body Weight may be performed per local institutional guidelines instead.

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

Cyclophosphamide Dose Adjustment for Pediatric Participants

For pediatric participants, where participant weight is >175% of the calculated ideal body weight (IBW) use the following formula to calculate cyclophosphamide dose:

$$\text{ABW} = \text{IBW} + 0.25 \times (\text{actual weight} - \text{IBW})$$

Estimation of Adujsted Body Weight may be performed per local institutional guidelines instead.

Use ABW in the calculation for body surface area (BSA).

Mesna

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

- 50% of cyclophosphamide daily dose (450 or 300 mg/m^2) divided into 4 doses at times 0 (start of cyclophosphamide infusion) and then 3 hours, 6 hours and 9 hours after the start of each cyclophosphamide infusion.

7.1.4 Lete-cel (GSK3377794) Infusion

Refer to the most current version of Lete-cel Investigator's Brochure regarding lete-cel and related clinical experience. Refer to the Drup Product and Infusion Manual for details and instruction on storage and administration of lete-cel.

Participants will receive a single dose of lete-cel four days after completing the lymphodepleting chemotherapy. This is considered Day 1 and all procedures and assessments to be performed are listed in the SoA. Supportive care guidelines are provided in Section 12.7.

Tocilizumab availability in institution's local pharmacy

A minimum of 2 doses of tocilizumab available for each participant will be required for administration within 2 hours after T-cell infusion, if needed for treatment of Cytokine Release Syndrome (CRS).

Premedication

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

Lete-cel (GSK3377794) Dose

The dose of lete-cel will be within the range of 1×10^9 – 15×10^9 transduced T cells, which will be administered by a single intravenous infusion on Day 1. The minimum transduced cell dose for meeting release criteria is 1×10^9.

If the transduced cell dose is less than the minimum dose required, manufacturing of additional transduced T cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range. In the event that no banked leukapheresis product is available, a second leukapheresis may be performed to achieve a dose in the target range.

Dosing of participants weighing less than 40 kg (including pediatric participants): For participants weighing less than 40 kg, lete-cel will be dosed per body weight with a range of 0.025×10^9 transduced cells/kg to 0.2×10^9 transduced cells/kg. The per body

weight adjusted dosing can only be manufactured from the intended commercial cell manufacturing process and participants weighing less than 40 kg will only be treated with intended commercial drug product supply, as soon as it becomes available. Screening of such participants may however begin before intended commercial drug product supply becomes available.

Pediatric participants weighing greater than or equal to 40 kg will be dosed per adult dosing.

Lete-cel (GSK3377794) Administration

On Day 1, the participant will receive thawed T cells by intravenous infusion. Prior to infusion, two clinical personnel in the presence of the participant, will independently verify and confirm that the information on the infusion bag is correctly matched to the participant, as per the sponsor's and clinical site's procedures.

The specific instructions for preparation and administration are found in the Drug Product and Infusion Manual.

Any deviation from the procedures detailed in the Drug Product and Infusion Manual should be recorded and reported accordingly.

In the event of adverse reaction to the cell infusion, the infusion rate should be reduced, and the reaction managed according to institutional standard procedures (Section 12.7). Steroid treatment should be avoided unless medically required. In the event a participant develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia.

The day of T-cell infusion may be delayed in participants with significant complications of lymphodepleting chemotherapy if according to the Investigator it is in the best interest of the participant. The timing of all assessments post-infusion will be calculated with reference to the T-cell infusion date. Participants who have undergone leukapheresis but do not receive the T-cell infusion will be replaced. Cytopenias alone should not be a reason to delay T-cell infusion unless complications are present (see Section 12.7 for guidance).

Vital signs will be recorded prior to the infusion (see SoA).

7.2 Preparation / Handling / Storage / Accountability

1. Deliveries of the investigational product are correctly received by a responsible person. Deliveries are recorded.
2. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study

interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

4. The participant's T-cell product received at the site from the manufacturer will be stored below -130°C until ordered by the Investigator (or designee) to be infused.
5. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of unused study intervention will be provided in the Study Reference Manual or Drug Product and Infusion Manual.

Precaution will be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the Investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable to this open-label substudy.

7.4 Study Intervention Compliance

Lete-cel will be intravenously administered to participants at the site per guidelines specified in the Drug Product and Infusion Manual. Administration will be documented in the source documents and reported in the eCRF.

7.5 Concomitant Therapy

Only chemotherapy (doxorubicin) and, if medically necessary for symptom management, palliative radiotherapy are allowed in the period between leukapheresis and lymphodepletion.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving starting at the time of screening for leukapheresis or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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

1. All prescription and non-prescription medication, vitamins, herbal and nutritional supplements taken by the participant during the 30 days prior to Screening for leukapheresis will be recorded at the Screening Phase visit.
2. All prior anti-cancer treatments taken by the participant must be recorded regardless of time.
3. All concomitant medications taken by the participant while in the Interventional Phase.
4. Use of any mutagenic agents or investigational agents must be reported.
5. Concomitant medications administered after the Interventional phase of the study will be recorded for SAEs and adverse events of special interest (AESIs).

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

7.5.1 Prohibited Concomitant Medication and Treatment

The following anti-cancer treatments are prohibited during the Interventional Phase of the study until PD is confirmed: non-protocol chemotherapy, immune therapy, biological therapy (including targeted therapies with tyrosine kinase inhibitors or monoclonal antibodies), or investigational anti-cancer therapy. Once PD has been confirmed following T-cell infusion, participants can receive therapy at the discretion of their healthcare provider while they remain in this study. This includes participation in other interventional clinical studies as needed.

During the Interventional Phase of the study until PD is confirmed participants should also not undergo other anticancer locoregional therapies, such as surgical resection, excisional biopsies or non-palliative radiation. Procedures intended for palliative care or symptomatic relieve on non-target lesions are permitted.

Systemic steroids may abrogate the effects of the T-cell therapy and therefore; are discouraged unless required to manage CRS (refer to Section 12.7 for CRS management) or other significant immune-mediated AEs. According to local standard of care or American Society of Clinical Oncology (ASCO) guidelines [Basch, 2010], steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the investigational product. Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

Systemic glucocorticoids are prohibited for any purpose other than to treat an event of suspected immunologic etiology (see Section 12.7). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants may receive other medications that the Investigator deems to be medically necessary in agreement with the Sponsor's Medical Monitor (or designee).

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Administration of live vaccine during the period of infusion of fludarabine, cyclophosphamide or lete-cel, and for at least 3 months after last

dose of any of these agents is prohibited. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the Investigator, the Sponsor and the participant.

7.5.2 Permitted Concomitant Medication and Treatment

Participants should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

Lesions that previously required radiotherapy should be recorded prior to lymphodepleting chemotherapy. Radiotherapy is not permitted after T-cell infusion until disease progression. However, in emergent clinical situations, palliative radiation for pain relief to non-measurable lesions or non-target lesions present at baseline may be permitted upon approval of Sponsor's Medical Monitor. However, lesions requiring radiotherapy after the T-cell infusion should be evaluated as to whether that indicates disease progression. These lesions are not suitable to be biopsied for biomarker analysis.

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

Permitted concomitant medications with required washout periods are listed Section 6.2, Table 6 of this Substudy. For therapies not already described in this protocol, washout periods must be around 5 half-lives, except for biologic agents for which a Sponsor consultation is required.

Once PD has been confirmed following T-cell infusion, participants can receive further therapy at the discretion of their healthcare provider while they continue to be followed in this study.

Recommendations for participants on therapeutic anticoagulants: [Maus, 2020]

- Before proceeding with lymphodepletion, participants on therapeutic anticoagulants should be switched from long-acting to short-acting formulations, wherever possible. Long-acting anticoagulants can significantly potentiate bleeding risk during CRS.
- If platelet counts drop below 100,000/μL in participants undergoing study treatment, dual-acting anticoagulants should be discontinued.
- If platelet counts drop below 50,000/μL in participants undergoing study treatment, all anticoagulants should be discontinued unless a patient has a recent thrombosis.

- If platelet counts drop below 50,000/μL in participants undergoing study treatment and the patient has a recent thrombosis, anticoagulants may be continued, but the dose should be reduced or platelet transfusions should be administered.

7.5.3 Rescue Medicine

Anti IL-6 drugs such as Tocilizumab may be administered to participants experiencing cytokine release syndrome (see Section 12.7.5 for details). Steroids may be used for emergent medical conditions. For all non-emergent conditions, consult with the Sponsor's Medical Monitor. Guidelines for management of complications are provided separately in the appendices.

See Section 12.7 for details on general supportive care that can be given during the study.

7.6 Dose Modification

Dose modification is not applicable to T cells. The entire dose of T cells that has been received by the site for the participant needs to be administered as a single dose. If a reaction occurs that does not allow safe administration of the full dose, the dose administered needs to be recorded.

If the transduced cell dose is less than the minimum dose required, manufacturing of additional transduced T cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range. In the event that no banked leukapheresis product is available, a second leukapheresis may be performed to achieve a dose in the target range.

7.7 Intervention after the End of the Study

No therapeutic intervention will be provided after the end of the study. Participant may receive any necessary treatment interventions from their oncologist.

8 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

Definitions and procedures for discontinuation of study intervention and participant discontinuation / withdrawal should follow the SoA in this Substudy and details outlined in Core Protocol Section 8.

9 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures should be performed per the SoA and as defined in the Core Protocol Section 9.

The following additional Substudy specific assessments should be performed per the SoA.

9.1 Interviews

9.1.1 Post T cell Infusion Interview

To evaluate T-cell infusion related experiences, symptoms and associated impacts, adult participants will be asked to participate in an optional telephone interview. Adult participants will be contacted about one week after infusion to set up a phone interview. The informed consent for this phone interview will be part of the clinical trial informed consent process. All of the interviews will be conducted by a trained interviewer will be audio recorded for transcription and analysis. Failure to complete the interviews will not constitute a protocol deviation.

9.1.2 End of Treatment Interview

To further evaluate disease and treatment related symptoms and associated impacts on function and health-related quality-of-life, adult participants will complete an optional Exit Interview conducted via telephone within approximately 21 days following completion of the last Interventional Phase visit and will focus on symptoms and impacts following discontinuation of study intervention. Failure to complete the interviews will not constitute a protocol deviation.

9.2 Patient Reported Outcomes

Patient reported outcomes will be assessed in adult participants as part of this protocol. The instruments in use in this section are only suitable for adult populations.

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9.3 Safety Assessments

Study assessments and procedures should be performed per the SoA and as defined in the Core Protocol Section 9.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical hypotheses

No formal statistical hypotheses are being tested in this substudy.

10.2 Sample size justification

Bayesian statistics will be employed to calculate the predictive probability [Lee, 2008] that the pooled overall response rate (ORR) will be ≥20% at the primary analysis (after the 10th treated participant across synovial sarcoma and myxoid/round cell liposarcoma has received T-cell infusion (modified Intent-To Treat [mITT] population) and has completed at least 2 post-baseline disease assessments since infusion or discontinued earlier) given the responses that have already been observed assuming a beta prior for the binomially distributed data. A weak prior beta (0.02, 0.08) is used, which is equivalent to the information present in 0.1 participant. If the predictive probability of 20 participants

treated in total that the response rate of ≥20% is less than 1% (i.e., 1 or less responders out of 10 participants at the primary analysis) is observed during the primary analysis, strong statistical evidence has been provided for no further development of the treatment for the target population. If the predictive probability of 20 participants treated in total that the response rate of ≥20% is greater than 90% (i.e., 6 or more responders out of 10 participants at the primary analysis) is observed during the primary analysis, strong statistical evidence has been provided in favor of further development of the treatment for the population. If the observed number of responders is between 2 and 5 at the primary analysis, this substudy may further enroll to treat 10 additional participants. The defined efficacy/futility thresholds are equivalent to the hypothetical study design: Bayesian predictive adaptive design [Lee, 2008] based on a historical response rate of approximately 20% versus a response rate of interest of 50% assuming 0.1 type I error and 80% power. Actual decisions will depend on the totality of the data including clinical activity, safety, PK, and biomarker data.

Populations for Analyses.

For purposes of analysis, the following populations are defined, the details of additional analysis populations will be defined in RAP:

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.
Safety Population	All participants who received any dose of lete-cel (GSK3377794).
Modified ITT (mITT) Population	All participants who received any dose of lete-cel.

10.3 Statistical Analyses

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	ORR, which includes confirmed complete or partial response as determined by Investigator assessment will be reported along with Clopper-Pearson exact 95% CI.
Secondary	PFS, DOR and TTR will be summarized using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant. DCR will be reported along with Clopper-Pearson exact 95% CI.

Endpoint	Statistical Analysis Methods
Exploratory	Will be described in the reporting and analysis plan.

Primary Efficacy Analysis

The primary analysis will be performed after all the enrolled participants have received T-cell infusion (mITT population) or withdrawn earlier and have completed at least 2 post-baseline disease assessments since infusion or discontinued earlier (due to death, loss to follow-up, or permanent study withdrawal).

Final Efficacy Analysis

The final analysis will be performed after all the treated participants have progressed or died or withdrew from the study.

ORR: Overall Response Rate (ORR) is defined as the percentage of participants with a confirmed CR or a PR relative to the total number of participants within the analysis population per RECIST v1.1 as determined by the local Investigators. At the primary analysis, ORR will be analysed based on mITT population.

ORR will also be reported in the ITT and mITT populations at the time of primary analysis for all participants.

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 at the primary analysis along with 95% Clopper-Pearson exact confidence interval (CI).

Secondary Efficacy Analysis

DCR: DCR, is defined as the percentage of participants within mITT population with a confirmed CR, PR, or SD with minimal 12 weeks duration relative to the total number of mITT participants at the time of primary analysis as determined by local Investigators per RECIST v1.1. The observed DCR will be reported along with 95% Clopper-Pearson exact CI.

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 outlined in RECIST v1.1, will be listed and summarized separately, as appropriate.

PFS: PFS, is defined as the time from the date of T-cell infusion until the earliest date of radiological PD as assessed by local Investigators per RECIST v1.1, or death due to any cause. For the analysis of PFS, if the participant received subsequent anticancer therapy prior to the date of documented events, PFS will be censored at the last adequate

assessment (e.g., assessment when visit level response was CR, PR, or SD) prior to the initiation of the new anticancer therapy. Progressive disease will also be defined per RECIST v1.1 criteria. Further details on rules for censoring will be provided in the RAP. PFS will be summarized using Kaplan-Meier quartile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant.

DOR: 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 RAP (Report analysis Plan).

TTR: TTR is defined as the time from the date of T-cell infusion to initial date of confirmed response (PR or CR) as assessed by local Investigators per RECIST v1.1 in the subset of participants who achieved a confirmed PR or CR.

TTR will be listed and summarized descriptively using median and quartiles in the subset of participants with a confirmed response of PR or CR.

Efficacy listings such as best overall response (BOR), DOR, PFS and OS will be reported for the mITT population (all participants who received lete-cel infusion at primary and final analysis data cut if data warrant).

Sensitivity Analysis

The analysis of primary endpoint, ORR, will also be performed among all participants in the ITT population.

10.3.2 Safety Analyses

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

Endpoint	Statistical Analysis Methods
Primary	AEs will be summarized using frequencies and proportions.
Secondary	AEs/SAEs/AESIs will be summarized using frequencies and proportions. RCL and instances of (IO will be summarized descriptively.
Exploratory	Will be described in the reporting and analysis plan

Safety data will be presented in tabular and/or graphical format and summarized descriptively.

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, if warranted, and across all on-treatment time points using a “worst-case” analysis. Complete details of the safety analyses will be provided in the RAP.

Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class and will be graded by the Investigator according to the NCI-CTCAE v5.0. In addition CRS and ICANS will be graded according to [Lee, 2019].

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

AEs of special interest will be further outlined in the RAP.

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

Clinical Laboratory Evaluations

Data for vital signs and ECGs will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the RAP.

Replication Competent Lentivirus (RCL) and instances of insertional oncogenesis (IO)

RCL and instances of IO will be summarized descriptively.

10.3.3 Other Analyses

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

10.3.4 Interim Analyses

Detailed interim safety and efficacy reports will be provided to the IDMC (see Section 5.4.1 of the Core Protocol) on a regular basis and the intervals will be specified in the IDMC charter.

SUBSTUDY 2: LETETRESGENE AUTOLEUCEL (LETE-CEL, GSK3377794) IN NY-ESO-1 POSITIVE PREVIOUSLY TREATED ADVANCED (METASTATIC OR UNRESECTABLE) SYNOVIAL SARCOMA OR MYXOID/ROUND CELL LIPOSARCOMA

Substudy Title: Evaluation of Safety and Antitumor Activity of Lete-Cel (GSK3377794) in HLA-A2+ Participants with NY-ESO-1 Positive Previously Treated Advanced (Metastatic or Unresectable) Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

TABLE OF CONTENTS

SUBSTUDY 2: LETETRESGENE AUTOLEUCEL (LETE-CEL, GSK3377794) IN NY-ESO-1 POSITIVE PREVIOUSLY TREATED ADVANCED (METASTATIC OR UNRESECTABLE) SYNOVIAL SARCOMA OR MYXOID/ROUND CELL LIPOSARCOMA

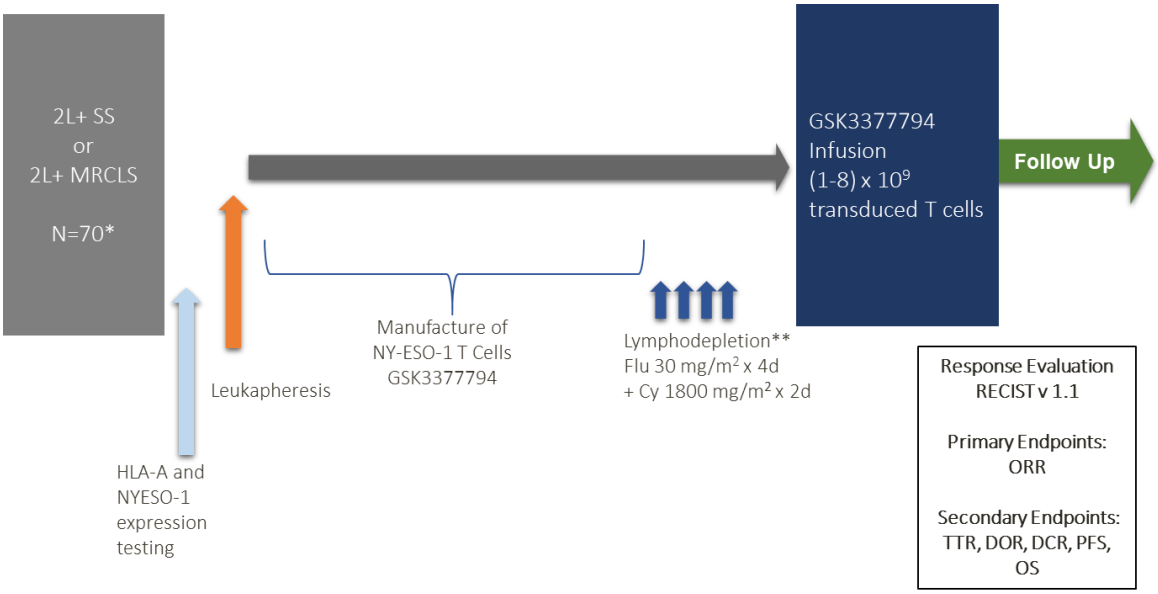
This previously treated (2L+) advanced (metastatic or unresectable) translocation-related sarcoma substudy contains substudy specific details. Refer to the body of the Core Protocol for all other information.

1 SYNOPSIS

This is a single-arm, non-randomized substudy to investigate the proposed commercial drug product supply process of letetresgene autoleucel (lete-cel, GSK3377794) in participants with advanced (metastatic or unresectable) NY-ESO-1 positive synovial sarcoma or myxoid/round cell liposarcoma, who have progressed following treatment with anthracycline-based chemotherapy, for the purpose of registration, as defined in the inclusion criteria (Section 6.1 of this Substudy). In this Substudy, we will not be evaluating tumors for LAGE-1a expression since the Immunohistochemistry assay used for the antigen detection recognizes NY-ESO-1 only and not LAGE-1a. LAGE-1a is rarely expressed in synovial sarcoma or myxoid/round cell liposarcoma.

Confirmation of disease progression from prior line of therapy will be required before lymphodepletion.

Substudy 2 Design



* The lymphodepleting regimen is to be adjusted as described in Section 7.1.3 of this Substudy.

See Section 1 Synopsis in the core protocol for overall study summary.

2 SCHEDULE OF ACTIVITIES (SOA)

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

Table 1 Substudy 2 Schedule of Activities – Screening and Leukapheresis

	Screening Phase[1]		Leukapheresis	Notes
	Target Expression Screening[2]	Leukapheresis Eligibility Screening, within 28 days prior to leukapheresis[3]		
Informed Consent for Screening	X			1. Written informed consent must be obtained prior to performing any study assessments or procedures, except as stated in footnote 12. Informed Consent for Leukapheresis and Treatment must be repeated if given more than 90 days prior to leukapheresis procedure. 2. This visit may be performed under a separate protocol when it is introduced. 3. Participants must be HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 positive tumor prior to conducting leukapheresis eligibility screening procedures. 4. Only collect this sample if optional Genetics Research Consent has been signed by the participant. Sample may be collected any time from signature of optional consent until leukapheresis. Liquid biopsy is a blood sample from which circulating cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes may be extracted. 5. Medical history will be recorded in the eCRF at Target Expression Screening and at Lymphodepletion Screening/Baseline visits; however, any changes in medical history must be recorded in source documents throughout the conduct of the study. 6. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported. 7. In pediatric participants height and weight will also be evaluated as a percentile vs national growth charts (based on sex and age) and vs genetic height target (expected height based on parental heights) and evaluation will be performed on whether growth is normal or abnormal. 8. To be performed within 7 days prior to the day of leukapheresis. 9. CD3 count prior to leukapheresis should be preferably performed within 24 hours from leukapheresis procedure.
Informed Consent for Leukapheresis and Treatment[1]		X		
Inclusion/Exclusion for Screening	X			
Inclusion/Exclusion for Leukapheresis		X		
Demographics	X			
Central Lab HLA -A genotyping[3]	X			
Tumor expression of NY-ESO- 1[3]	X			
Liquid biopsy (blood)[4]	X			
Medical History[5]	X	X		
Prior/Concomitant Medications[6]	X	X	X	
Height and Weight[7]		X		
Physical Exam (complete)		X	X[8]	
ECOG or Lansky or Karnofsky[10]	X	X		
Vital Signs[11]		X	X[8]	
12-lead ECG (in triplicate)		XXX	XXX[8]	
ECHO/MUGA		X[12]		
CT / MRI		X[13]		
Brain MRI[14]		X[13]		
Hematology		X[12]	X[8]	
Clinical Chemistry		X[12]	X[8]	
Coagulation Tests		X[12]	X[8]	
Lymphocyte Subset (CD3/CD4/CD8)		X[8]	X[8,9]	
Estradiol and FSH, if needed to determine CBP		X		
Pregnancy Test[15]		X[15]	X[15]	

	Screening Phase[1]		Leukapheresis	Notes
	Target Expression Screening[2]	Leukapheresis Eligibility Screening, within 28 days prior to leukapheresis[3]		
Urinalysis		X[12]	X[8]	10. Lansky will be used for participants <16 years of age; Karnofsky will be used for participants ≥16 and <18 years of age; and ECOG will be used for participants ≥18 years of age. 11. Includes temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. 12. ECHO/MUGAand laboratory assessments performed as standard of care prior to study consent will be acceptable as long as assessment is done within 28 days before leukapheresis. 13. CT/MRI scan performed as standard of care prior to study consent will be acceptable as long as assessment is done within 90 days before leukapheresis. Any FDG PET/CT performed as part of clinical routine within 90 days before leukapheresis, will also be collected. 14. In addition to the Brain MRI, MRI of the spine will be performed when clinically indicated. 15. WOCBP must have a highly sensitive negative urine or serum pregnancy test at screening for leukapharesis and within 24 h prior to leukapheresis. 16. Includes HIV, HBV, HCV, HTLV, EBV, CMV, and syphilis (spirochaete bacterium). 17. See Section 6.1 Table 5 for specifics on renal assessment. 18. SAEs and AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or leading to study withdrawal will be collected from signing informed consent for target expression screening. All SAEs and AEs will be collected starting at leukapheresis (See Section 9.4.1 in the Core Protocol).
Infectious disease markers[16]		X[12]		
Creatinine clearance by GFR or 24h urine[17]		X		
Adverse Events and Serious Adverse Events	X[18]	X[18]	X	
Leukapheresis			X	

AE=adverse event; CBP=child-bearing potential; CT = computerized tomography; EBV = Epstein Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FDG = Fluorodeoxyglucose; FSH=follicle-stimulating hormone; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV =

human immunodeficiency virus; HTLV = human T-lymphotropic virus; MRI = magnetic resonance imaging; MUGA = multigated acquisition; SAE=serious adverse event; WOCBP = Women of childbearing potential

Table 2 Substudy 2 Schedule of Activities – Interventional Phase (Lymphodepletion and Treatment)

	Treatment Fitness & Eligibility / Baseline	Lymphodepletion				T-cell Infusion[1]	Post T-cell Infusion												
Month (1 month = 4 weeks)	-1					1								2				3-6	Q3M from month 9 until confirmed PD
Week (Week N visit for N≥1 is scheduled on 1st day of the week = Day 7N-6)	-3 to -2	-1				1					2	3	4	5	6	7	8	10, 12, 18, 24 or until confirmed PD, whichever is sooner	
Day	-17 to -8	-7	-6	-5	-4	1	2	3	4	6	8	15	22	29	36	43	50	64, 78, 120, 162	
Visit Window	N/A								±1 day					±3 days				±7 days	±1 month
Treatment Fitness and Inclusion/Exclusion for Treatment Eligibility	X																		
Request lete-cel shipment	X[2]																		
Med. History[3]	X																		
Physical Exam (complete)	X	X				X	X	X	X	X	X		X			X	X	X	X
Physical Exam (dedicated)												X		X	X				
Prior/Con Meds[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG, Lansky, or Karnofsky[5]	X					X					X		X		X		X	X	X
Developmental exam and puberty assessment[6,7]	X																		X[8]
Vital Signs[9] and weight[7]	X	X	X	X	X	X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECHO/MUGA[11]	X																		
Pulse oximetry						X[12]	X	X	X	X	X	X[13]	X	X[13]		X	X	X	

	Treatment Fitness & Eligibility / Baseline	**Lymphodepletion**				**T-cell Infusion[1]**	**Post T-cell Infusion**												
Month (1 month = 4 weeks)	**-1**					**1**								**2**				**3-6**	**Q3M from month 9 until confirmed PD**
Week (Week N visit for N≥1 is scheduled o[n] 1st day of the week = Day 7N-6)	**-3 to -2**	**-1**				**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**	
Day	**-17 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**6**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**64, 78, 120, 162**	
Visit Window	**N/A**								**±1 day**					**±3 days**				**±7 days**	**±1 month**
12-lead ECG[14]	XXX					X			X		X								
CT/MRI[15]	X														X			X[16]	X[16]
Brain MRI[17]	X[17]																		
ICE or CAPD[18]						X[19]	X	X	X	X	X								
Chest X-Ray	X																		
Hematology[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Uric acid	X					X										X			
Creatinine clearance by GFR or 24 h urine[21]	X																		
Coagulation Tests[20, 22]	X					X	X	X	X	X	X	X							
Ferritin[20]	X																		
Troponin and NT-proBNP / BNP[20,23]	X																		
Pregnancy	X					X[24]							X				X	X[25]	X[25]
Urinalysis[26]	X		X	X	X														
Infectious disease markers[27]	X																		
CMV IgG and PCR[28]	X					X						X		X		X			
Thyroid function tests	X																		
CRP[20]	X					X			X		X	X	X	X	X	X	X	X	X

	Treatment Fitness & Eligibility / Baseline	**Lymphodepletion**				**T-cell Infusion[1]**	**Post T-cell Infusion**												
Month (1 month = 4 weeks)	**-1**					**1**								**2**				**3-6**	**Q3M from month 9 until confirmed PD**
Week (Week N visit for N≥1 is scheduled o[n] 1st day of the week = Day 7N-6)	**-3 to -2**	**-1**				**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**	
Day	**-17 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**6**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**64, 78, 120, 162**	
Visit Window	**N/A**								**±1 day**					**±3 days**				**±7 days**	**±1 month**
Adverse Events and Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transgene Copies (Persistence for Safety) and VSV-G DNA (RCL)[29]	X																	weeks 12 and 24	Month 12 and Q6M[30]
Genetic sample	X																		
Survival follow-up																		X	X
Lymphodepletion																			
Fludarabine		X[31]	X	X	X														
Cyclophosphamide			X	X	X														
Investigational Product Administration																			
Lete-cel (GSK3377794)						X													
Patient-Reported Outcomes[32]																			
Healthcare Resource Utilization[33]	X	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Post-lete-cel infusion interview (adult participants only)											X[34]								
EOT interview (adult participants only)																			X[35]

	Treatment Fitness & Eligibility / Baseline	Lymphodepletion	T-cell Infusion[1]	Post T-cell Infusion														
Month (1 month = 4 weeks)	**-1**		**1**									**2**				**3-6**	**Q3M from month 9 until confirmed PD**	
Week (Week N visit for N≥1 is scheduled o[n] 1st day of the week = Day 7N-6)	**-3 to -2**	**-1**	**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**			
Day	**-17 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2**	**3**	**4**	**6**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**64, 78, 120, 162**
Visit Window	**N/A**								**±1 day**					**±3 days**				**±7 days**	**±1 month**

CCI [redacted]

1. On Day 1, all samples will be collected and assessments performed prior to T-cell infusion (within 24 h), unless otherwise specified.
2. As lete-cel needs to be on site prior to lymphodepletion, request lete-cel no later than 4 working days prior to the day of lymphodepletion. The mechanism of request will be provided in Apheresis and Drug Product and Infusion Manual.
3. Medical history will be recorded in the eCRF at Treatment Eligibility Screening / Baseline visit; however, any changes in medical history must be recorded in source documents throughout the conduct of the study.
4. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.

5. Lansky will be used for participants <16 years of age; Karnofsky will be used for participants ≥16 and <18 years of age; and ECOG will be used for participants ≥18 years of age.
6. To be assessed in pediatric participants only.
7. In pediatric participants height and weight will also be evaluated as a percentile vs national growth charts (based on sex and age) and vs genetic height target (expected height based on parental heights) and evaluation will be performed on whether growth is normal or abnormal.
8. To be assessed once a year.
9. Vital signs include temperature, blood pressure, pulse rate, and respiratory rate.
10. Vital signs on day of T-cell infusion should be taken pre-infusion, and approximately at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
11. If suspected CRS Grade ≥2, an ECHO/MUGA is required at onset of Grade ≥2 CRS. Additional monitoring must be conducted (including inpatient continuous cardiac telemetry monitoring) for a minimum of 3 days post onset and as long as deemed necessary by the Investigator (refer to Section 12.7.5).
12. On T-cell infusion day, pulse oximetry should be taken pre-infusion, and approximately at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
13. Pulse oximetry at these visits will be performed if medically indicated.
14. ECG can also be performed at other time points if medically indicated. Triplicate ECG will be collected at Treatment Eligibility Screening / Baseline visit and single ECGs at other timepoints. Participants with an increased burden of cardiovascular risk factors (as per Section 9.3.6) will undergo evaluation by a cardiologist prior to lymphodepletion.
15. See Section 9.1.1 of the core protocol for scan description and areas to scan. If a participant is found to have a tumor response or PD by imaging and considered to be clinically stable by iRECIST criteria (see Section 12.6.2), a follow-up confirmation scan must be done no earlier than 4 weeks and no later than 8 weeks following the scan when response or PD first seen. A participant is not considered to have a response or PD until follow-up scan confirms the finding.
16. CT/MRI will not be performed at Week 10. CT/MRI assessments only need to continue until confirmed PD.
17. Brain MRI should be performed at baseline if more than 4 months have elapsed from last MRI. Brain MRI will be performed at other time points, if clinically indicated. MRI of the spine will be performed, if clinically indicated.
18. All participants will be monitored as shown in the SoA. 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. It can also be used at later visits if indicated. In participants < 12 years of age, CAPD should be used in place of ICE.
19. To be administered prior to T-cell infusion.
20. If CRS and/or ICANS is suspected, chemistry, hematology, ferritin, coagulation and CRP tests should be performed locally every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed. In addition, if CRS is suspected, cytokine samples will be collected for central analysis following same schedule (as per SOA Table 3 footnote 4).
21. See Section 6.1 Table 5 for specifics on renal assessment.
22. Coagulation tests include INR, PTT or aPTT and fibrinogen. Coagulation tests should be taken at baseline, and on Days 1, 2, 3, 4, 6, 8 and 15.
23. Troponin and NT-proBNP / BNP tests should be monitored for participants with CRS Grade ≥2 as clinically indicated.
24. WOCBP must have a negative urine or serum pregnancy test prior to lete-cel infusion.
25. WOCBP will need to have pregnancy tests performed at all visits indicated in the table for the duration of the contraception period (Section 6.1 of this Substudy).
26. In addition to the specified time points, urinalysis will be done at other timepoints if warranted by the symptoms.
27. Includes HIV, HBV, HCV, HTLV, EBV, and syphilis (spirochaete bacterium).
28. Only participants who are CMV IgG seropositive at Baseline will continue to be monitored for CMV viremia by CMV DNA PCR post Baseline. CMV will also be assessed if GBS is suspected.
29. If possible, this sample also needs to be obtained in case of any SAE that occurs after T-cell infusion.

30. If no gene modified cells are detected for two consecutive assessments post-infusion, and the participant is ≥2 years post T-cell infusion, samples for VSV-G DNA (RCL) and persistence of gene modified cells will be discontinued (Section 9.3.9.1 of the Core Protocol).
31. On Day -7. fludarabine will not be administered to participants ≥60 years old.
32. Patient-Reported Outcomes instruments are only for adult participants.
33. Only perform until PD is confirmed. Site staff will complete the paper Healthcare Utilization Worksheet and enter data in the eCRF.
34. Contact participant about one week after T-cell infusion to schedule the phone interview to be conducted by Day 21 of the study. If phone interview cannot be scheduled at this time, contact participant every two weeks until successful or the 60-day limit is reached from T-cell infusion. Beyond 60 days from T-cell infusion, no need to conduct the participant interview as recall may not be reliable.
35. To be conducted within approximately 21 days following the last visit in the Interventional Phase.
36. To be administered prior to infusion.

BNP = B-type natriuretic peptide; CAPD= Cornell Assessment of Pediatric Delirium; CMV = Cytomegalovirus; Con Meds = concomitant medications; CRS=cytokine release syndrome; CT = computerized tomography; EBV = Epstein Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; CCI [redacted] = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE=Immune Effector Cell-Associated Encephalopathy; Med history=medical history; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NT-proBNP = N-terminal pro-BNP; PCR = Polymerase chain reaction; PD=progressive disease; CCI [redacted] Q3M = every 3 months; RCL=replication competent lentivirus; TSH = Thyroid stimulating hormone; VSV-G =vesicular stomatitis virus G protein; WOCBP = Women of childbearing potential.

Table 3 Substudy 2 Schedule of Activities – Immunogenicity and Biomarkers (Interventional Phase)

	Sample Type	Baseline	Lymphodepletion				T-cell infusion					Post T-cell infusion							
Month (1 month = 4 weeks)		-1					1								2			3-6	Q3M from month 9 until confirmed PD[1]
Week		-3 to -2	-1				1					2	3	4	5	6	8	(10)[2], 12, 18, 24 or until confirmed PD, whichever is sooner[1,2]	
Day		-17 to -8	-7	-6	-5	-4	1[3]	2	3	4	6	8	15	22	29	36	50	(64)[2], 78, 120, 162	
Visit Window		N/A								±1 day					±3 days			±7 days	±3 months
Cell phenotype and Functional Assays	PBMC	X								X		X	X	X		X	X	X	X
Transgene Copies (Persistence)	PBMC	X					X	X		X		X	X	X		X	X	X	X
Cytokine Analyses[4]	Serum	X					X	X	X	X	X	X	X	X		X	X	X	X
TGF-β analyses	Plasma	X					X					X	X	X		X		X	X
Anti-lete-cel Antibodies	Serum						X						X			X	X	Week 12, 24	Month 9, 12, 18, 24, 30, 36
Liquid biopsy (blood)[5]	Plasma	X										X		X		X		X	X
Tumor Biopsy[6]	Biopsy	X[7]												X[8]				X[9]	

1. All assessments need to be performed at all visits specified in the Table, up to the visit establishing confirmed PD or study withdrawal or discontinuation.
2. Assessments should match imaging (Body CT/MRI) visits; consequently PK, immunogenicity and Biomarker samples will not be collected at Week 10.
3. All assessments to be performed prior to T-cell infusions
4. If CRS is suspected, serum for cytokine analysis should be collected for research every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.
   Notes:
   - For scheduled visits where a cytokine sample collection is already requested, there is no need to collect an additional sample from the CRS collection kit that day.
   - Chemistry, hematology, ferritin, coagulation and CRP tests should also be performed locally following same schedule (as per SOA Table 2 footnote 20).
5. Blood sample from which circulating cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes may be extracted.

6. Biopsies for research are at Baseline, at Week 4, and at disease progression, with the exception of participants for whom there is no safely accessible tumor tissue. In addition to the indicated collection times, tumor biopsies can be obtained at any time during the study execution.
7. The Baseline biopsy should be collected anytime within 28 days prior to the start of lymphodepleting chemotherapy. An archived FFPE block from a biopsy 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).
8. Week 4 biopsy must be taken preferably between D21-23 if medically visibile, but window for collection is extended until Week 6 visit (D39).
9. Must be taken once at confirmed disease progression if medically feasible.

PBMC=peripheral blood mononuclear cell; PD=progressive disease; Q3M = every 3 months.

Table 4 Substudy 2 Schedule of Activities – Follow-up after Disease Progression

Substudy 2: Completion of Interventional Phase Follow-up[1]												
Time post lete-cel infusion	**Year 1** [2]			**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Years 6-15** [3]
Months (1 month = 4 weeks)	3	6	12	18	24	30	36	42	48	54	60	Annually
Visit window	± 2 weeks		± 3 month									± 6 months
Safety Assessments												
Medical History and Physical Exam including Weight [4]		X	X	X	X	X	X	X	X	X	X	X
Mutagenic agents, other investigational agents or anti-cancer therapies		X	X	X	X	X	X	X	X	X	X	X
Adverse Events and Serious Adverse Events [5]		X	X	X	X	X	X	X	X	X	X	X [6]
Pregnancy test for WOCBP [7]	<==========X[7]==========>											
Hematology [8]		X	X		X		X		X		X	
Serum chemistry [8]		X	X		X		X		X		X	
Developmental exam, height[4] and puberty assessment in pediatric participants			X		X		X		X		X	
Laboratory Assessments												
Transgene Copies (Persistence) for safety VSV-G DNA (RCL) for safety [8,9]		X	X	X	X	X	X	X	X	X	X	X [9]
Other Assessments												
Survival Status [10]		X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]												

1. If a site visit is not feasible, then medical evaluation of participants may take place via telemedicine (e.g. phone call or video conferences) where country and/or local regulations allow. Where applicable country and local regulations and infrastructure for home healthcare allow, upon approval by the sponsor, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include medical history, physical exam, collection of blood samples, measurement of height and weight. Remote visits may be performed upon approval by the sponsor at the participant's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary.
2. Assessments for the Year 1 will be conducted per Table 2 and Table 3 until disease progression.

3. Participants who do not have persistence of gene modified cells may be followed remotely during years 6-15.
4. New medical history/medications/chemotherapies. In pediatric participants height and weight will also be evaluated as a percentile vs national growth charts (based on sex and age) and vs genetic height target (expected height based on parental heights) and evaluation will be performed on whether growth is normal or abnormal.
5. Adverse Event and Serious Adverse Event collection is limited to:
    a. New malignancies
    b. New incidence or exacerbation of a pre-existing neurologic disorder
    c. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
    d. New incidence of a hematologic disorder
    g. New incidence of infections (potentially related to gene-modified cell therapy)
    e. Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy
6. During years 6-15 of annual follow-up period, AEs and SAEs will be entered in the CRF if reported by the participants or investigator.
7. For Women of child bearing potential (WOCBP), pregnancy testing should be conducted during contraception period only as defined in Section 5.1 of this substudy. When pregnancy testing is performed at visits where hematology sample is collected, blood pregnancy testing will be done. At visits where hematology sample is not collected, urine pregnancy test is acceptable unless serum testing is required by local regulation or IRB/IEC.
8. If a visit for medical evaluation is conducted via telemedicine, a site visit to collect a blood samples should be performed as soon as practicable.
9. If no gene modified cells are detected for 2 consecutive assessments post infusion, and the participant is ≥2 years post T-cell infusion, all laboratory assessments including persistence and RCL may be discontinued (Section 9.3.12 of the Core Protocol).
10. If a participant is contacted between the scheduled visits, the date of last contact should be recorded as an unscheduled visit.

CCI [redacted]

Abbreviations: CCI [redacted]; EOT=end of treatment; CCI [redacted]; RCL=replication competent lentivirus; VSV-G =vesicular stomatitis virus G protein.

3 INTRODUCTION

3.1 Substudy 2 Background and Rationale

See Core Protocol Section 3.2 for background information on TCR approach, NY-ESO-1, and letetresgene autoleucel (lete-cel, GSK3377794).

For evaluation of the proposed commercial cell manufacturing process of lete-cel in translocation-related sarcomas of synovial sarcoma (SS) and myxoid/round cell liposarcoma (MRCLS), this substudy will enroll participants with advanced (metastatic or unresectable) SS or MRCLS, who have progressed following treatment with anthracycline-based chemotherapy.

This substudy is intended for registration purposes and will enroll and treat the defined number of participants using proposed commercial vector/cell manufacturing process. This substudy will use the intended commercial drug product supply once it is available and the regulatory document has been amended accordingly to support this supply.

This substudy has been designed to generate efficacy and safety data for lete-cel in participants ≥10 years of age who have previously treated, advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma expressing the NY-ESO-1 antigen, who are HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06 allele positive.

Soft Tissue Sarcomas (STS) are a heterogeneous group of connective tissue cancers originating from mesenchymal cells and their precursors [Blay, 2014] representing ~1% of all cancers in adults worldwide each year and accounting for ~2% of cancer related mortality [Singer, 2000; Amankwah, 2013]. STS consists of approximately 50 histological subtypes [Amankwah, 2013], each with distinct specific characteristics, including differential chemo-sensitivity.

Synovial Sarcoma:

Synovial sarcoma is a rare malignancy accounting for approximately 5–10% of all STS [Riedel, 2018; Noone, 2018; Brennan, 2016; Honoré, 2015]. The estimated incidence of synovial sarcoma is 0.15 per 100,000 in the US and 0.14 per 100,000 in the UK [Wang, 2017; Stacchiotti, 2018; Brennan, 2016]. Approximately one-third of synovial sarcoma occurs in childhood, with a peak incidence in the third decade of life [Ferrari, 2008]. The European Paediatric Soft Tissue Sarcoma Study Group conducted a prospective trial exploring the incidence and outcome of synovial sarcoma in European patients [Ferrari, 2015]. From August 2005 to August 2012, 138 patients <21 years old with synovial sarcoma were registered from 60 centers in 9 European countries. The median age at diagnosis was 13.7 years. Of the 138 participants included in this study, 29 (21%) were <10 years of age and 109 (79%) were ≥10 years of age.

Synovial sarcoma is a life-threatening disease with a 5-year overall and cancer-specific survival of 50-60% in adult patients [Spillane, 2000; Lewis, 2000; Singer, 2000]. For patients presenting with localised disease, standard treatment consists of a wide surgical excision or radical surgery of the primary tumor, combined with adjuvant radiotherapy

for intermediate-high grade tumors and deep tumors >5 cm in diameter. There is no clear role of neoadjuvant and adjuvant chemotherapy in high risk patients. Approximately 50% of patients with synovial sarcoma will develop metastatic disease [Ten Heuvel, 2009; Krieg, 2011], and the survival for patients developing metastatic disease is 12-15 months. These rates have not improved over the last 2 decades.

Myxoid/Round Cell Liposarcoma (MRCLS):

Myxoid/round cell liposarcoma is a subtype of liposarcoma which is associated with specific translocations, t (12;16)(q13;p11) or t (12;22)(q13;q12) and represents about 30-35% of liposarcomas and 5-10% of all adult STS [WHO, 2002]. In the 2013 edition of the WHO classification, the term "round-cell liposarcoma" was removed as the prognosis and the frequency of metastasis in patients with myxoid liposarcoma is related to the degree of cellularity of the tumor rather than the presence of round cells vs spindle cells. In addition, the same molecular abnormalities are found in both round-cell and spindle-cell morphologies of high-grade myxoid liposarcoma [Doyle, 2014]. Therefore, patient diagnoses of "high grade myxoid liposarcoma" and "myxoid/ round cell liposarcoma" are equivalent when assessing patients for eligibility for this study, in accordance with the WHO 2013 classification [IARC WHO Classification of Tumours, No 5, Fletcher 2013].

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

Myxoid tumor types have relatively favorable prognoses, with an ~80-90% 5-year survival rate but tumors with a round-cell component >5% have a poor prognosis with a 5-year survival rate of ~50-75% because they recur locally and tend to metastasize quickly and widely [Smith, 1996]. The median time from diagnosis to metastases is 35 months.

Treatment involves the wide surgical excision of the tumor and surrounding tissue; high-grade round cell liposarcoma may be treated with pre-operative chemotherapy and/or pre- operative or post-operative radiotherapy [NCCN, 2012]. Radiotherapy decreases the incidence of local relapse but chemotherapy may not prevent metastatic occurrence nor improve survival [Moreau, 2012; Hoffman, 2013].

Treatment options for patients with advanced MRCLS have been evaluated. In a retrospective analysis of trabectedin in advanced pre-treated MRCLS (in which 46 of the 51 patients had received anthracycline and ifosfamide either in combination or in sequence), a response rate of 51% was reported [Grosso, 2007]. A randomized, open-label, active-controlled trial comparing trabectedin (n=345) treatment with dacarbazine (n=173) in patients with unresectable, locally advanced or metastatic leiomyosarcoma (73%) or liposarcoma (27%) (dedifferentiated, myxoid round cell, or pleomorphic) and previous treatment with an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen demonstrated an overall response rate (ORR of 7% (CI 4.3, 9.8) with trabectedin, an improvement of median progression-free survival

(PFS) of 4.2 (CI 3.0, 4.8) vs 1.5 (CI 1.5, 2.6) months on dacarbazine but no difference in overall survival [Yondelis prescribing information 2015]. Eribulin demonstrated an improvement in survival (median OS 13.5 vs 11.5 months; HR= 0.768; 95% CI, 0.618; 0.954) compared with darcarbazine in subjects with liposarcoma and leiomyosarcoma who received 2 or more prior lines of therapy. There was no difference in PFS and ORR was 3.9% with Eribulin and 4.9% with darcarbazine [Schöffski, 2015].

GSK pilot study 208469 is an ongoing open label, Phase I/II pilot study of lete-cel in ≥2L myxoid/round cell liposarcoma with NY-ESO-1 positive tumors expressing the antigen in ≥30% cells at 2+/3+ by immunohistochemistry in subjects with HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 allele [D'Angelo, 2017].

The 208469 protocol completed accrual of the first cohort of 10 treated subjects, treated under the initial lymphodepletion regimen. Treatment with NY-ESO-1c259T-cells in MRCLS appears to have an acceptable safety profile consistent with other NY-ESO-1c259T-cell studies [D'Angelo, 2018a; D'Angelo, 2018c]. Biomarker analyses including peak persistence, expression of serum cytokines and of activation markers post infusion were reported [Van Tine, 2019a; Van Tine, 2019b]. Final analysis is on-going.

Standard first-line treatment in patients with advanced, unresectable, or metastatic synovial sarcoma consists of anthracycline chemotherapy as single agent or as part of combination regimens (e.g., doxorubicin with ifosfamide), which induces responses in 20-30% [Spurrell, 2005; Sleijfer, 2010; Vlenterie, 2016]. Two years ago, Lartruvo (olaratumab) received accelerated FDA approval as 1L treatment in combination with doxorubicin for metastatic soft tissue sarcoma (STS) [Lartruvo USPI, 2016]. However, recently the confirmatory trial (ANNOUNCE study) did not demonstrate any survival benefit nor any improvement in response rates (18%) over standard chemotherapy, and therefore, the study failed to meet its primary endpoint [Tap, 2019]. Accordingly, the approval for this agent has been recended in the US and EU. A review of the medicine has now been initiated by the regulators (US/EU) and its approval status has been rescinded.

Dacarbazine is also authorised in some countries in the EU for the advanced soft tissue sarcoma as a part of combination chemotherapy and dacarbazine monotherapy response rates range from 4% to 6% in prospective studies [Dacarbazine SmPC, 2015].

After failure of anthracycline-based chemotherapy, few options exist for patients to be treated in second-line setting. These patients have poor clinical outcomes with currently available treatments.

Pazopanib (Votrient) is authorised by EMA and by FDA for treatment of patients with metastatic STS who have failed prior chemotherapy. However, response rates in synovial sarcoma are low, ranging from 4% to 13%, and this offers no improvement in overall survival [Votrient SmPC, 2018; Votrient USPI, 2017]. Trabectedin (Yondelis) is approved in the EU for patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Trabectedin (Yondelis) is also approved in the US for select histological subtypes of STS (liposarcoma and leiomyosarcoma). Efficacy data are based mainly on liposarcoma and leiomyosarcoma and demonstrated overall response rates of <10% in Phase 3 studies

[Yondelis SmPC, 2012; Yondelis USPI, 2015]. While the registration studies with trabectedin did not include synovial sarcoma patients, in a Phase 2 study, synovial sarcoma patients treated with trabectedin demonstrated an ORR of about 10% [Sanfilippoa, 2015]. Trabectedin has also not been shown to improve survival in any sarcoma population.

Thus clear unmet medical need exists for treatment options in this population.

3.2 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks as well as reasonably expected adverse events of lete-cel (GSK3377794) may be found in the Lete-cel Investigator's Brochure. It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation as these studies are designed to provide information about the safety and effectiveness of investigational medicines. This section outlines the potential benefits, risks and the mitigation strategy for this study.

3.2.1 Risk Assessment

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Lymphodepleting Chemotherapy (Fludarabine/Cyclophosphamide)		
• Myelosuppression • Immunosuppression • Bone Marrow Failure and Infection • Cardiotoxicity • Pulmonary Toxicity • Urinary Tract and Renal toxicity • Veno-occlusive disease • Secondary Malignancy • Hyponatraemia • Neurotoxicity	Cases were reported with both drugs.	Please refer to the prescribing information of fludarabine and cyclophosphamide and Section 12.7.
• Autoimmune haemolytic anaemia • Autoimmune thrombocytopenia • Decreased vision • Peripheral neuropathy	Cases were reported with fludarabine	Please refer to the prescribing information of fludarabine.
Lete-cel (GSK3377794)		
Cardiac arrest	Potential risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been 2 reports of unexpected fatal cardiac arrest. The first occurred 5 months after T-cell infusion and was confounded by hypotension due to poor oral intake and concurrent renal insufficiency. The second occurred approximately 1 week after T-cell infusion in the setting of a recent fungal catheter line infection, concurrent treatment with caspofungin and multifocal pneumonia / edema seen on chest CT.	Participants with significant cardiac risk factors or with CRS $\geqslant$ Grade 2 will receive close cardiac monitoring (Core Section 9.3.6 and Section 12.7.5). Participants with lung metastases should be considered for pulmonary consultation prior to lymphodepletion ; participants deemed at high risk of pulmonary complications should be monitored closely (Core Section 9.3.7). Central lines should be closely monitored for infection (Core Section 12.7.2). Systemic fungal infections are excluded (Substudy 2 Exclusion 9) Monitoring of risk of increased cardiac toxicity with the use of anti-microbials (Core Section 12.7.2.6)
Cytokine release syndrome (CRS)	Identified risk due to TCR T-cell infusion considered adverse event of special interest (AESI)	Participants with pre-existing autoimmune disorders are excluded (Section 6.2 of this Substudy). Management for

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
		CRS is described in Section 12.7.5. Events Grade ≥3 must be reported as SAEs and submitted to GSK within 24 hours.
Graft versus host disease (GVHD)	Identified risk associated with TCR T cells reacting against normal tissues and organs considered an AESI	Participants with pre-existing autoimmune disorders are excluded (Section 6.2). Management for GVHD is described in Section 12.7.6.
Haematopoietic cytopenias (including Pancytopenia/aplastic with bone marrow failure/anemia)	Identified risk associated with lymphodepletion chemotherapy and TCR-T cell infusion considered an AESI	Participants with cytopenias are excluded (Section 6.2 of this Substudy). Management for pancytopenia is described in Section 12.7.7.
Haemorrhage secondary to thrombocytopenia	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been reports of haemorrhage (including intracranial and pulmonary) in participants with severe and prolonged thrombocytopenia.	Protocol guidance on Blood product support provides recommendation on platelets levels to be maintained in the in-patient setting and the out-patient setting, as per Section 12.7.3.
Hypersensitivity	Identified risk due to TCR-T cell infusion. Hypersensitivity reactions (including anaphylaxis) may be due to the 5% (v/v) DMSO inTCR-T formulation.	Participants with history of allergic reactions to any agents used in the study are excluded. See Section 6.2 for details. Participants will be premedicated against potential infusion reactions with antihistamines on the day of TCR-T cell infusion. See Section 7.1.4 for details.
Reactivation of previous viral infections after prolonged leukopenia	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion	Participants who have received radiation to bone marrow that would predispose them to prolonged cytopenia after lymphodepletion (in the investigator's opinion) are excluded. See Section 6.2 for details. Lymphodepletion dose will be modified in participants with potentially reduced bone marrow reserve. See Section 7.1.3 for details. Participants with active infection are excluded. Participants with CMV seropositivity will be monitored regularly for viral reactivation. For HSV/VZV prophylaxis, participants will receive acyclovir or valacyclovir for one year from LD. Prophylaxis will be given to those with HBV seropositivity. See Section 6.2 and Core Section 12.7.2 for details.

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Neutropenia (including fatal neutropenia)	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion	Patients are excluded based on absolute neutrophil counts (Section 6.1.1). Investigator must discuss with Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in participants at risk (Section 7.1.3). G-CSF to be administered in accordance with ASCO guidelines or institutional practice (Section 7.1.3). Dose modifications are included for fludarabine and cyclophosphamide (Section 7.1.3) Grade 4 Neutropenia events lasting ≥28 days must be submitted to GSK within 24 hours (Core Section 9.4.7).
Decreased Vision	Potential risk: There was a report of decreased vision in a patient who received lete-cel infusion following lymphodepletion with fludarabine and cyclophosphamide.	Dose reductions for fludarabine for renal impairment are included (Section 7.1.3). Investigator must discuss with Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in patients at risk (Section 7.1.3)
Guillain-Barré syndrome (GBS) / Acute inflammatory demyelinating polyneuropathy	Potential risk associated with TCR T-cell infusion. Two participants who received lete-cel developed GBS.	Participants with prior or active demyelinating disease will be excluded (Section 6.2 of this Substudy). Neurologic consultation is required for participants with Grade 2 or higher neurologic events of a ≥7 day duration. Any potential future recurrence of GBS will lead to a pause in study enrollment until further investigation.
Treatment-related inflammatory response at tumor site(s)	Identified risk associated with TCR T-cell infusion	Routine monitoring and testing as clinically required.

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Potential risk associated with inflammation in the brain following TCR infusion. There have been reports of ICANS in participants who received lete-cel.	Participants with brain metastases with features associated with increased risk of ICANS are excluded (Section 6.2 of this Substudy). Monitoringcriteria for ICANS are described in Section 12.7.8.
Insertional oncogenesis	Potential risk in T cells transduced with lentiviral vector	Routine PV. To be monitored in the LTFU Protocol.(208750) or LTFU portion of this study. Monitoring to follow the recommendations set forth in the FDA guidance, 2020a. PBMC samples are used as a surrogate sample for monitoring insertional oncogenesis by polymerase chain reaction (PCR) for gene modified cells in the blood.
Replication competent lentivirus (RCL)	Potential risk associated with use of lentivirus	Routine PV. To be monitored in the LTFU Protocol. Samples will be tested for the presence of VSV-G DNA copies (Section 9.3.11 of the Core Protocol).
On/Off-Target Off-Tumor Risks	Potential risk associated with use of lentivirus	To be monitored in this protocol and in the LTFU Protocol. Protocol includes eligibility criteria (Section 6.1 and Section 6.2 of this Substudy), routine PV, and management strategies as appropriate to limit, diagnose, characterize and treat toxicities related to potential risks (Section 12.7).
Study Procedures		
Tumor biopsy	Bleeding, pain, swelling associated with the procedure	Biopsies are performed by trained personnel; image-guided when necessary and performed only if deemed safe.
Leukapheresis	Electrolyte imbalance and bleeding at the site of phlebotomy	Refer to local site procedures and guidelines.

The goal of the risk management measures is to maximize the chance of therapeutic benefit while mitigating and better understanding the risks of treatment with lete-cel.

The known safety profile of lete-cel is based on 166 enrolled and 125 treated participants as of 27 January 2021 as decribed in Lete-cel Investigator's Brochure. The most commonly reported treatment-emergent adverse events which occurred in ≥50% of participants following lete-cel infusion were leukopenia/WBC decreased (81%), neutropenia/neutrophil count decreased (80%), nausea (78%), anemia/RBC decreased (78%), thrombocytopenia/platelet count decreased (77%), fatigue (70%), pyrexia (66%), diarrhea (57%), and lymphopenia/lymphocyte count decreased (54%). The most common Grade 3 and 4 AEs which occurred in ≥20% of participants following lete-cel infusion were leukopenia/WBC decreased (78%), neutropenia/neutrophil count decreased (74%), thrombocytopenia/platelet count decreased (62%), anemia/RBC decreased (58%), lymphopenia/lymphocyte count decreased (52%), febrile neutropenia (36%), and hypophosphatemia (27%). These AEs are consistent with expected immediate adverse events after lymphodepletion chemotherapy.

Across all studies, 47 (38%) participants had SAEs considered by the Investigator to be related to study treatment. Treatment-related SAEs occurring in more than 2 subjects following lete-cel infusion were: cytokine release syndrome (CRS) (15%), pyrexia (6%), neutropenia/neutrophil count decreased (5%), rash/rash maculo-papular (4%), thrombocytopenia/platelet count decreased (4%) and febrile neutropenia (3%). For the 16 participants who received a second infusion, five treatment related SAEs were reported after second T-cell infusion, which included 1 (6%) case each of CRS, cytomegalovirus infection, embolism, febrile neutropenia, and rash/rash maculo-papular.

Among the adverse events of special interest,

1. CRS was reported in 52 (42%) cases (of 125) as of 27 January 2021 across all lete-cel clinical trials. Of these, there was 1 participant with Grade 4, 9 with Grade 3, 21 with Grade 2, and 19 with Grade 1. There were a total of 19 cases of CRS that were reported as SAEs. All 19 SAEs resolved in 2 weeks or less. Five cases of the 19 reported SAEs were treated with tocilizumab. Median duration of the CRS events was 8-9 days (range 1-28 days).
2. A total of 7 cases (of 125) of GvHD have been reported of which 3 cases were reported as an SAE. All cases were Grade 1-3, occurred in patients with multiple myeloma, and completely recovered with supportive treatment. Six (6) out of 7 participants with reported GvHD were from Study 209393 (formerly ADP-01411) which required an allogeneic stem cell transplant prior to the T-cell infusion.
3. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), originally named as 'encephalopathy' was reported in 1 case with multiple brain metastasis, that was transient, and resolved in 2 days with supportive care.
4. Five (5%) participants had reported treatment-emergent AE of pancytopenia (3 participants: 2 with Grade 3, and 1 with Grade 1) or bone marrow failure (2 participants: 1 with Grade 5 fatal, and 1 with Grade 2) (refer to Lete-cel Investigator's Brochure for details).

5. GBS has been reported in 2 participants, both of which completely recovered with standard gamma globulin treatment.

To date, none of the analyses for insertional oncogenesis and replication competent lentivirus have been positive.

Pediatric Participants

This substudy allows pediatric participants 10 years of age or older. Previously, 2 pediatric participants have been treated in Study 208466 (ADP-04511). The first was a 15-year-old white hispanic female treated in Cohort 3 of the study in which a milder, cyclophosphamide only containing lymphodepletion regimen was used prior to T-cell infusion; and this participant achieved PR after the first infusion, progressed 9 months following treatment, and received a second infusion and achieved stable disease, and she died in September 2018, nearly 2 years after initial treatment with GSK3377793. The second participant was a 12-year-old white female enrolled into Cohort 2; which included participants with tumors that have low NY-ESO-1 expression levels and received a high dose cyclophosphamide and fludarabine containing lymohodepletion regimen prior to lete-cel infusion. This participant achieved SD as her best response, subsequently progressed 8 months following lete-cel treatment, and died 11 months after lete-cel treatment.

As of 24 February 2019, a total of 29 AEs were reported for both pediatric participants as definitely or probably related to lete-cel. A total of 14 Grade 4 AEs (5%) were reported, none of which were reported as being related to lete-cel. The first participant experienced 2 SAEs: acute cholecystitis and CMV infection. Neither event was reported as related to study drug, and both events resolved. There were no SAEs reported by the second participant. There were 5 events of cytokine release syndrome reported. All events were Grade 1 or 2, and all have resolved. Overall, the observed AEs are similar to those observed in adult participants treated with lete-cel, with the vast majority consistent with events observed as a result of the lymphodepletion regimen.

3.2.2 Benefit Assessment

As of 27 January 2021, 125 participants have been treated with lete-cel. Objective responses have been observed in the ongoing synovial sarcoma study (208466/ADP-04511) and in multiple myeloma post-autologous transplant study (209393/ADP-01411) [Lete-cel Investigator's Brochure].

In Cohort 1 of study 208466 (which is similar to the treatment regimen and participant population proposed for this protocol), a single infusion of GSK3377794 demonstrated an encouraging response rate of 50% (6/12 participants, 95% CI: 0.21-0.79), with an encouraging durability of response of 30.9 weeks (95% CI: 14-72) and one participant demonstrating a complete response. Importantly, the responses induced after T-cell infusion were associated with a median survival of approximately 24 months, which represents a marked improvement over a median survival of 12 months in relapsed metastatic synovial sarcoma.

Objective responses have been observed in 21 (84%) out of 25 of participants in multiple myeloma after autologous transplant (study 209393/ADP-01411) [Lete-cel Investigator's Brochure].

Additionally, 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 synovial sarcoma. The estimated overall three and five-year survival rates for patients with synovial sarcoma were 38% and 14%, respectively [Robbins, 2015].

More recently, responses have also been observed in patients with myxoid round cell liposarcoma (MRCLS , study 208469) [D'Angelo, 2018a], thereby demonstrating encouraging clinical activity of lete-cel across multiple NY-ESO-1 and LAGE-1a expressing tumor types.

3.2.3 Overall Benefit/Risk Conclusion

Treatment with letetresgene autoleucel (lete-cel, GSK3377794) has been well tolerated in 103 participants with different tumor types [Lete-cel Investigator's Brochure]. Toxicities associated with engineered T-cell infusion, specifically CRS, have been observed in less than one-third of the treated participants, were of low grade, and managed with supportive care in the majority of cases. To date, lete-cel has demonstrated an AE profile that has generally been manageable and acceptable in the context of benefit/risk assessment.

In view of the clinical responses observed in relapsed, refractory patients, and as per the risk asseement presented above, the benefit/risk ratio supports continued development of lete-cel in NY-ESO-1-positive synovial sarcoma, myxoid/round cell liposarcoma and other solid tumors of high unmet medical need.

4 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of lete-cel in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 positive advanced synovial sarcoma or myxoid/round cell liposarcoma	Overall Response Rate (ORR) per RECIST v1.1 by central independent review in the full analysis set of participants treated with commercial vector supply and cell manufacturing processes
Secondary - Efficacy	
To further evaluate the efficacy of lete-cel in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 positive advanced synovial sarcoma or myxoid/round cell liposarcoma	• Overall Response Rate (ORR) per RECIST v1.1 assessed by Investigators • Time to Response (TTR) • Duration of Response (DoR) • Disease Control Rate (DCR)

Objectives	Endpoints
	• Progression Free Survival (PFS) • Overall Survival (OS)
Secondary - Safety	
To evaluate the safety and tolerability of lete-cel in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 participants with NY-ESO-1 positive advanced synovial sarcoma or myxoid/round cell liposarcoma	• Frequency and severity of Adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in protocol) • Laboratory parameters • Replication Competent Lentivirus (RCL) • Instances of Insertional oncogenesis (IO)
To evaluate potential immune response to lete-cel.	• Presence and titers of anti-GSK3377794 antibodies over time
Secondary - Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 specific (c259) T cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit
Exploratory / Other	

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	

AE/s = adverse event/s; AESI/s: adverse event/s of special interest; AUC (0-t) = area under the time curve from zero to time t; Cmax = maximum concentration; DOR = duration of response; HLA = human leukocyte antigen; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; Tmax = Time to Cmax; TTR = Time to Response.

5 STUDY DESIGN

5.1 Overall Design

Study 208467 Substudy 2 is a multicenter, open-label study evaluation of the safety and efficacy of letetresgene autoleucel (lete-cel, GSK3377794) in participants with synovial sarcoma or myxoid/round cell liposarcoma.

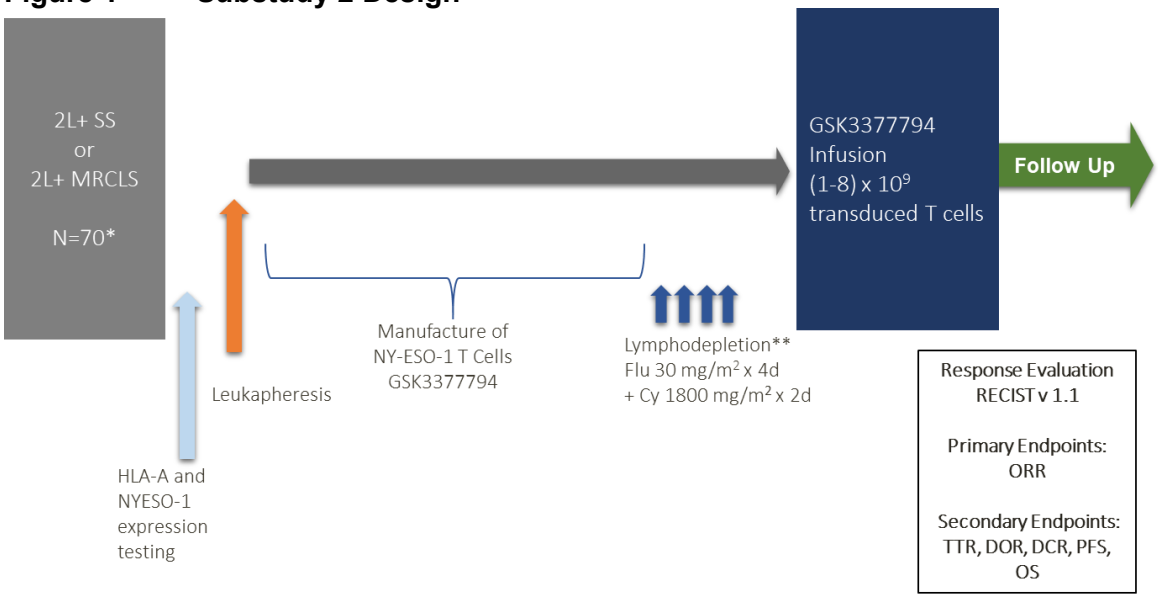
For evaluation of lete-cel proposed commercial cell manufacturing process in synovial sarcoma and myxoid/round cell liposarcoma, this substudy will enroll participants with advanced (metastatic or unresectable) NY-ESO-1^{+} synovial sarcoma or myxoid/round cell liposarcoma who have progressed following treatment with anthracycline-based chemotherapy. This substudy will consist of at least 60 participants dosed with the intended commercial vector supply and manufacturing processes who have completed a minimum of 6-month follow-up or have died or have withdrawn early following lete-cel treatment. This substudy will enroll the number of participants needed to obtain 60 treated with intended commercial vector supply and manufacturing process for the primary analysis population (approximately 72).

Participants identified by the Investigator as possible candidates for the substudy must have completed HLA-typing and preliminary target expression screening for NY- ESO-1 antigen expression; participants with the HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 alleles whose tumor expresses the NY-ESO-1 antigen above the cut-off according to the applied immunohistochemistry assay are eligible to undergo further screening for this study.

It is intended that the data from Substudy 2 will be used to support registration of lete-cel in synovial sarcoma and myxoid/round cell liposarcoma. T cells infused to participants within Substudy 2 to support this registration will be generated using the intended commercial vector supply and cell manufacturing processes (application supplement to be submitted). Substudy 2 may initiate screening prior to the availability of the intended commercial vector supply and cell manufacturing process.

This study allows that participants weighing greater than or equal to 40 kg and identified as eligible for treatment prior to availability of the intended commercial vector supply and cell manufacturing processes may receive treatment with the clinical drug product supply. Any such participants will be counted separately to ensure that at least 60 participants are treated with intended commercial drug product supply for the intended analysis population PEAP. Drug product supply type (‘clinical’ vs ‘commercial’) will be recorded in the CRF as part of the route of synthesis.

Figure 1 Substudy 2 Design



* Approximately 72 out of 87 will be enrolled on intended commercial drug product supply in order to ensure that at least 60 participants will receive lete-cel using intended commercial vector supply and manufacturing process.

** The lymphodepleting regimen is to be adjusted as described in Section 7.1.3 of this Substudy.

Participants will undergo stepwise enrollment on the study followed by treatment according to defined phases within the study (See Figure 2 Participant Journey Schema below) which will include:

Part 1: Screening

1) Target expression screening for the presence of HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 type and tumor expression of NY ESO-1,

   (Note: If a participant was previously tested for HLA and/or NY-ESO-1 expression under a different GSK-sponsored protocol, testing of HLA and/or NY-ESO-1 for 208467 may not be required dependent on the test platform(s) used and whether they meet the 208467 protocol requirements [see Section 6.3 of the Core Protocol])

2) Leukapheresis screening phase to determine eligibility for undergoing leukapheresis beginning up to 28 days prior to the day of leukapheresis,

Part 2: Leukapheresis/Manufacture

3) Leukapheresis procedure,

   (Note: leukapheresis may have been performed under another GSK-sponsore protocol or substudy of this protocol)

Part 3: Lymphodepletion/Treatment

4) Treatment fitness assessment and eligibility confirmation including confirmation of disease progression from last line of treatment, per RECIST v1.1,

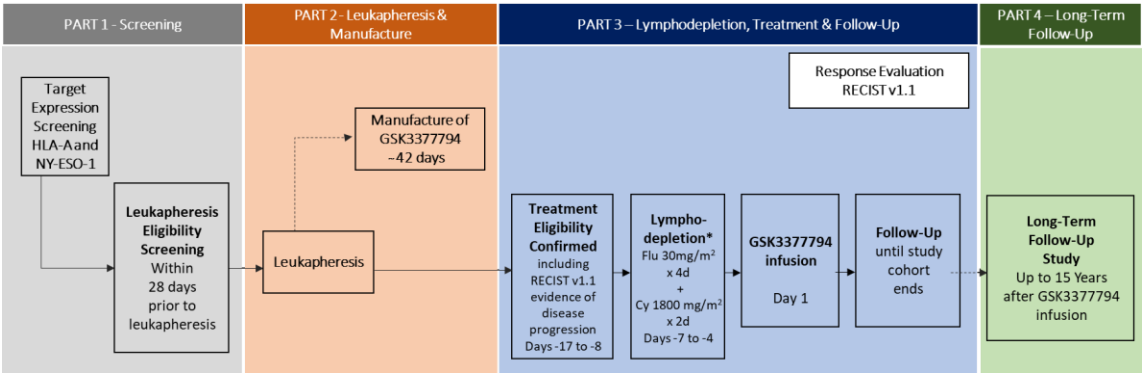
5) Interventional phase including Lymphodepletion from Days -7 to -4, lete-cel infusion on Day 1 and follow-up until the end of study (as defined in Section 5.3 of this Substudy),

(Note: TCR engineered T-cell 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 lete-cel infusion.

Figure 2 Participant journey Schema



* The lymphodepleting regimen is to be adjusted as described in Section 7.1.3 of this Substudy.

Part 1: Screening

See Core Protocol Section 5 of this Substudy for complete details of screening approach. Inclusion / exclusion criteria are listed in Section 6.

In this substudy enrolling participants with advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, participant screening may start at any time after diagnosis of advanced disease. Participants may also be screened upon relapse of metastatic disease.

Disease progression may be present but is not mandatory for screening. Screening will consist of two phases: target expression screening and leukapheresis eligibility screening.

For target expression 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 expression will also be evaluated on tumor tissue from a formalin-fixed and paraffin-embedded (FFPE) archival (most recent preferred) or fresh biopsy (see Tumor biopsies section below for more details). 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.

Note: target expression Screening may also be performed under a separate Screening protocol such as athe GSK molecular disease characterization initiative (MDCI) study (213299), or under other NY-ESO-1/LAGE-1a T-cell protocols.

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

Supportive chemo- or radio-therapy may be administered between leukapheresis and lymphodepletion if a participant cannot be treatment-free. Mandatory washout periods prior to start of NY-ESO-1-Specific (c259) T-cell infusion must be respected (See Section 6.2 of this Substudy).

Part 2: Leukapheresis/Manufacture

The initiation of leukapheresis procedure constitutes enrollment in the study. The collected T cells will be sent for manufacturing.

See Core Protocol Section 5 for complete details of leukapheresis and manufacture approach, including use of supportive chemo- or radio-therapy between leukapheresis and the start of lymphodepletion.

Part 3: Lymphodepletion/Treatment

See Core Protocol Section 5 for complete details of lymphodepletion and treatment approach. For this substudy, confirmation of disease progression per RECIST v1.1 is required prior to lymphodepletion.

Part 4: LTFU

See Core Protocol Section 5 for complete details of the long term follow up study. See end of substudy definition in Section 5.3 of this Substudy for details of participant transition to LTFU.

Tumor Biopsies

Archival tumor FFPE or fresh biopsy from a representative tissue is required from all participants to be used for antigen expression (NY-ESO-1) eligibility screening. If multiple archival samples are available, then the most recent archival sample should be used. If fresh biopsy is performed, then this tissue should be used:

a. Formalin-fixed paraffin embedded (FFPE) tumor specimens in paraffin blocks are preferred. A minimum of 20 unstained slides (5-micron serial fresh cut) is required as an alternative. Patients with fewer than 20 unstained slides may still be considered for screening following discussion with Medical Monitor
b. Acceptable specimens include core needle biopsies from deep tumor tissue (minimum three cores x 18G or larger and approximately 1 cm long) or excisional, incisional punch or forceps biopsies for cutaneous, subcutaneous or mucosal lesions
c. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavages are not acceptable
d. Tissue should have been obtained from 1 year of consent and be of good quality on the basis of total and viable tumor unless discussed with Medical Monitor

A pre-treatment tumor sample collected within 28 days prior to initiating lymphodepletion is required for Substudy 2. This biopsy will be used as baseline for biomarker 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 bridging or standard of care intermediate anti-cancer therapy, the screening biopsy will be used for baseline.

Additional biopsies will also be collected at Week 4 and at disease progression. In exceptional cases, where such biopsies cannot be collected, these may be deferred in consultation with the sponsor. These cases include participants for whom there is no safely accessible tumor tissue; or if conducting such a biopsy would compromise the medical condition of the participant; or if other clinical considerations preclude conduct of the biopsy procedure. In addition to the indicated collection times, tumor biopsies can be obtained at any time during the study execution.

See Core Protocol Section 9.9.1 for other biopsy considerations.

5.2 Number of Participants

Substudy 2 will enroll approximately 87 participants previously treated with anthracycline-based regimen for advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, including :

- Approximately 15 participants expected to receive the clinical drug product supply;
- Approximately 72 participants planned to receive intended commercial drug product supply in order to ensure that at least 60 participants will receive letetresgene autoleucel (lete-cel, GSK3377794) using commercial vector supply and manufacturing process and who have completed a minimum of 6-month follow-up or have died or have withdrawn early following treatment.

This study allows pediatric participants 10 years of age or older.

5.3 End of Study Definition

5.3.1 End of Substudy for Individual Participants

a) End of **Interventional phase** for individual participants

A participant is considered to have completed the Interventional phase of the Substudy when one of the following occurs (whichever is sooner):

- Participant has confirmed disease progression (also need to ensure that participant is followed for SAEs through 90 days following T-cell infusion, or 30 days following T-cell infusion if the participant initiates new anticancer therapy, whichever is earlier);
- Participant dies;
- Interventional phase ends for the Substudy (See Section 5.3.2 of this Substudy).

If participant withdraws consent or is withdrawn for other reasons prior to end of their Interventional phase, they will be considered early withdrawal.

b) End of **Follow-up phase** for individual participants

All participants who are alive at the end of the Interventional phase will enter a follow-up phase and will remain in the Follow-up phase until one of the following occurs (whichever is sooner):

- Participant dies;
- Substudy ends (See Section 5.3.2 of this Substudy).

If participant withdraws consent or is withdrawn for other reasons prior to end of their Follow-up phase, they will be considered early withdrawal.

All participants alive after the end of the Follow-up phase, will be followed in a separate long term follow up (LTFU) protocol (GSK study 208750) for observation of delayed AEs and survival for a duration of 15 years post-T-cell infusion in accordance with FDA [FDA, 2020a] and EMA guidance [EMA, 2009]. If LTFU protocol is not yet available at the particular clinical site, participants may be temporarily followed per LTFU schedule under this protocol (Section 2 Table 4 of this Substudy) until LTFU protocol becomes available. The transfer of any individual participant to the LTFU protocol 208750 should not exceed 6 months.

5.3.2 End of Substudy

a) End of **Interventional phase**:

The interventional phase ends when the total number of participants dosed will have confirmed disease progression or died or have been lost to follow-up or withdrawn early.

b) End of **Follow-up phase**:

The Follow-up phase ends when 70% of the total number of participants who received at least the minimum target dose of lete-cel (mITT) have died or have been lost to follow-up, to allow for mature data on overall survival (OS).

All participants alive after the end of the Follow-up phase of the Substudy, will be followed in a separate long term follow up (LTFU) protocol (GSK study 208750) for observation of delayed AEs and survival for a duration of 15 years post-T-cell infusion in accordance with FDA [FDA, 2020a] and EMA guidance [EMA, 2009]. If LTFU protocol is not yet available at the particular clinical site, participants may be temporarily followed per LTFU schedule under this protocol (Section 2 Table 4 of this Substudy) until LTFU protocol becomes available. The transfer of any individual participant to the LTFU protocol 208750 should not exceed 6 months.

c) End of **Substudy**:

The substudy ends when all treated participants have transferred to the separate LTFU protocol (GSK study 208750), declined consenting to the LTFU protocol, completed LTFU requirement in this study, have been lost to follow-up, or withdrawn early, or died.

5.4 Scientific Rationale for Substudy Design

This substudy has been designed to generate efficacy and safety data for lete-cel in participants ≥10 years of age who have previously treated, advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma, whose tumor expresses the NY-ESO-1 antigen and who are HLA-A*02:01, HLA-A*02:05, or HLA-A*02:06 allele positive. The single arm design has taken into consideration that:

1. Synovial sarcoma and myxoid/round cell liposarcoma are rare, life-threatening diseases of which the target population for lete-cel is a small subset.
2. After failure of anthracycline-based chemotherapy, currently available therapies to treat synovial sarcoma or myxoid/round cell liposarcoma do not provide adequate disease control and no approved products for this targeted population exist.
3. Compelling data from pilot Studies 208466 (for synovial sarcoma) and 208469 (for myxoid/round cell liposarcoma) indicate that lete-cel may offer a meaningful advantage over available 2L therapies.

This substudy will enroll approximately 72 participants to support the primary analysis consisting of at least 60 participants treated with intended commercial drug product supply who have completed a minimum of 6-months follow-up or have died or have withdrawn early following lete-cel treatment. The over-enrollment takes into account an estimated 5-10% dropout to achieve 60 participants for the PEAP population.

5.5 Justification for Dose

5.5.1 Justification of Lymphodepleting Regimen

Based on prior experience with lete-cel in participants with synovial sarcoma and melanoma, where similar lymphodepletion regimen was associated with optimal responses [Merchant, 2015; D'Angelo, 2018b], the lymphodepleting regimen for participants treated under protocol amendments 1-5 has been to administer fludarabine, 30 mg/m^2/day × 4 days (Day -7 to -4) and cyclophosphamide, 1800 mg/m^2/day × 2 days (Day -5 to -4), with lete-cel infusion on Day 1.

Based on additional safety data (prolonged neutropenia; fatal neutropenia [see Lete-cel Investigator's Brochure] and modelling data, to further optimize lymphodeletion and reduce potential for acute and prolonged cytopenias while also minimizing impact on efficacy, the cyclophosphamide cumulative dose is modified from 3600 to 2700 mg/m^2. The fludarabine dose remains unchanged.

This regimen was previously used in Study 208469 (Cohort 2) in MRCLS, and the dosing is currently in use for NSCLC participants in Study 208471 (slightly different schedule).

The refined lymphodepleting regimen for participants treated as of protocol amendment 6 is as follows:

- Fludarabine, 30 mg/m^2/day × 4 days (Day -7 to -4) and cyclophosphamide, 900 mg/m^2/day × 3 days (Day-6 to -4), with lete-cel infusion on Day 1.

Rules for further dose reductions on cyclophosphamide are also adapted by applying the same 33% reduction as previously used (in protocol amendments 1-5) as follows:

- As of protocol amendment 6, a standard reduction for cyclophosphamide dose (in mg/m^2) of $2700 = 900 \times 3$ days is to use $1800 = 600 \times 3$ days.

5.5.2 Justification of lete-cel (GSK3377794) Dose

A dose range of 1×10^9 to 8×10^9 total transduced T cells had initially been chosen as it was within the cell dose in which clinical responses were observed without significant toxicity in previous clinical trials and which was logistically feasible to manufacture (based on initial assumptions related to yield).

At this target dose, lete-cel has resulted in objective responses in participants with metastatic synovial sarcoma, metastatic melanoma [Robbins, 2015], and multiple myeloma [Rapoport, 2015] whose tumors expressed the NY-ESO-1 or LAGE-1a antigens and who met the HLA inclusion criteria.

This cell dose range was included in protocol amendments 1 through 5.

Optimization of the dose range:

A cell dose of 15×10^9 transduced T cells represents the updated upper end of what is logistically deemed feasible to manufacture.

As such, the upper end of the target dose range of transduced T cells is increased from 8×10^9 to 15×10^9 in order to maximize the delivery of cells for participants whose manufacture yields $>8 \times 10^9$ transduced T cells.

Patients have previously been treated at this upper end of the revised dose range: in two older pilot studies (synovial sarcoma Study 208466 and multiple myeloma Study 209393), 3 patients received doses $>8 \times 10^9$ (up to 14.4×10^9) transduced T cells with no safety signals identified.

Other TCR T cells have been reported safe at even higher doses: the genetically engineered T cells with a TCR targeting human papilloma virus-associated epithelial cancer HPV-16 E7 (E7 TCR) were reported in a first-in-human, phase 1 clinical trial of 12 participants, to not show any dose limited by toxicity with a maximum dose of 100×10^9 engineered T cells administered [Nagarsheth, 2021].

Since no dose-toxicity relationship has been established todate on 125 patients dosed with lete-cel (see Lete-cel Investigator's Brochure), it is anticipated that the safety profile in patients who receive doses up to the theoretical 15×10^9 transduced cells will remain comparable to the current safety profile.

- For participants treated as of protocol amendments 6, any released manufactured product counting between (1-15) $\times 10^9$ transduced cells will be shipped in its entirety for infusion as a single dose.

Due to the sample size and tight control over product release, participants receiving doses $>8 \times 10^9$ will be closely monitored with ongoing review by the SRT.

6 STUDY POPULATION

Inclusion/Exclusion criteria *for the registration substudy are grouped into 3 parts and eligibility screening will take place in the following 3 steps:*

- ***Target Expression Screening:*** *A set of criteria permitting participants' blood to be screened for HLA-type and an archival or fresh tumor sample to be screened for the expression of NY-ESO-1.*
- ***Leukapheresis Eligibility Screening:*** *To be fulfilled prior to performing leukapheresis procedure.*
- ***Treatment eligibility screening:*** *To be fulfilled prior to starting lymphodepletion.*
  - ***Treatment fitness (for safety):*** *To be evaluated prior to commencing lymphodepleting chemotherapy and administration of lete-cel (GSK3377794).*

6.1 INCLUSION CRITERIA

6.1.1 *Target Expression Screening*

*Participants are eligible to be screened for target expression (HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1) only if all of the following criteria apply:*

1. Capable of giving signed informed consent including compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol. For participants <18 years of age (or the legal minimum age in the relevant country) their legal guardian must give informed consent. Pediatric participants will be included in age-appropriate discussion in order to obtain assent.
2. Participant must be ≥10 years of age at the time of signing the informed consent. Participant scheduled to receive *clinical* drug product supply must also weigh ≥40 kg. For participant scheduled to receive intended *commercial* drug product supply and weighing <40kg, the Investigator must also consult with the Medical Monitor prior to inclusion.
3. Participant has a diagnosis of synovial sarcoma or myxoid/round cell liposarcoma, confirmed by local histopathology with evidence of disease-specific translocation.

   Note: Evidence of a relevant disease-specific translocation is required at latest prior to leukapheresis (Inclusion 8).
4. Participant has advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma. Unresectable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise.
5. Male or female. Contraception requirements will apply at the time of leukapharesis and treatment.
6. A representative tumor tissue specimen (archived or fresh biopsy) with associated pathology reportshould be available to perform NY-ESO-1 antigen expression analysis, unless a recent NY-ESO-1 expression test result from the same designated

central laboratory, following the same procedures, has already been performed under a separate GSK-sponsored protocol or under another substudy. For guidance on acceptable specimen material see Tumor Biopsies under Section 5.1.

6.1.2 *Leukapheresis Eligibility Screening*

Prior to finalizing participant treatment plan, please note that bridging/standard of care anti-cancer therapy is allowed under Section 7.1.2 conditions but that there are washout requirements prior to leukapheresis and prior to lymphodepletion. Additional considerations should be given to accumulated radiotherapy prior to lymphodepletion. All the Inclusion Criteria in Section 6.1.1 must apply again prior to leukapheresis. In addition, the following criteria must also apply:

7. Life expectancy ≥24 weeks
8. Participant has confirmed evidence of a relevant disease-specific translocation per below:
   - For *synovial sarcoma*, presence of a translocation involving chromosome 18 (SYT gene) and/or chromosome X (SSX1, SSX2 or SSX4 genes);
   - For *myxoid/round cell liposarcoma*, presence of a translocation involving chromosome 12 (DDIT3 gene) and/or chromosome 16 (FUS gene) and/or chromosome 22 (EWSR1 gene).

   Note: Methods, such as, but not limited to, fluorescence in situ hybridization (FISH) assay or Next Generation Sequencing (NGS) or Immuno HistoChemistry (IHC) using fusion-specific antibody are commonly used to detect translocations.
9. Participant is either currently being treated with or has completed at least one standard-of-care treatment including anthracycline-containing regimens (e.g., doxorubicin alone, doxorubicin with ifosfamide) for advanced (metastatic or inoperable) disease. Participants who are intolerant to anthracycline may receive ifosfamide alone unless intolerant to or ineligible to receive ifosfamide. Participants who received anthracycline-based therapy in the neoadjuvant/adjuvant setting and progressed will be eligible.

   NOTE: Participants "intolerant" to a chemo-radiotherapy are those who EITHER are ineligible to receive chemotherapy due to poor functional status OR have developed a Grade ≥3 toxicity necessitating discontinuation of chemotherapy or dose modification, and/or unplanned hospitalization to alleviate effects of toxicity [Van Abbema, 2019].

   NOTE: Participants with advanced (metastatic or unresectable) disease can also undergo leukapheresis prior to initiating first line or standard therapy.
10. Participant must be positive for HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles by a validated test in a designated central lab prior to leukapheresis.

    NOTE: If a participant was previously tested for HLA type under a different GSK-sponsored protocol, testing of HLA type for 208467 may not be required dependent on the test platform(s) used and whether they meet the 208467 protocol requirements [see Section 6.3 of the Core Protocol]).

11. Participant's tumor has been pathologically reviewed by a designated central laboratory with confirmed positive NY-ESO-1 expression defined as ≥30% of cells that are 2+ or 3+ by immunohistochemistry.

    NOTE: If a participant was previously tested for NY-ESO-1 expression under a different GSK-sponsored protocol, testing of NY-ESO-1 expression for 208467 may not be required dependent on the test platform(s) used and whether they meet the 208467 protocol requirements [see Section 6.3 of the Core Protocol]).

12. Left ventricular ejection fraction ≥45% with no evidence of clinically significant pericardial effusion.

13. Performance status: for participants <16 years of age, Lansky >60, or for participants ≥16 and <18 years of age, Karnofsky >60, or for participants ≥18 years of age, Eastern Cooperative Oncology Group (ECOG) of 0-1.

14. Participant must have adequate organ function and blood cell counts, within 7 days prior to the day of the leukapheresis procedure, as indicated by the following laboratory values in Table 5.

Table 5 Definitions of Adequate Organ Function

System	Laboratory Value
Hematological[a,b,c]	
Absolute Neutrophil count (ANC)	≥1.5 x10^9/L (without granulocyte colony-stimulating support)
Absolute Lymphocyte count (ALC)	≥0.5 x 10^9/L
Hemoglobin	≥8 g/dL or ≥5.0 mmol/L (without transfusion support)
Platelets	≥ 100 x10^9/L (without transfusion support)
Renal	
Creatinine clearance ≥40 mL/min • Participants who are ≥18 and <65 years of age must be assessed either: o by 24-hour urine creatinine collection OR o by using Serum Creatinine (Scr) via an estimated creatinine clearance (CrCl) calculated as outlined below by using the CKD-EPI equation and adjusting the result by multiplying with (BSA/1.73) to obtain CrCl in mL/min: Step 1: estimated glomerular filtration rate (GFR) to be obtained from the Chronic kidney disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009]: **Estimated GFR** (mL/min/1.73m^2) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 *[if female]* × 1.159 *[if black]* *where*: Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min(Scr/κ,1) indicates the minimum of Scr/κ or 1, max(Scr/κ,1) indicates the maximum of Scr/κ or 1, and Age is in years. Step 2: correction factor to be applied per the American National Kidney Foundation in order to obtain the estimated creatine clearance in mL/min **Estimated CrCl** (mL/min) = **Estimated GFR** (mL/min/1.73 m^2) × **BSA (m^2) / 1.73** To calculate the BSA for fludarabine dosing, use actual body weight. An adjusted body weight (ABW) may be required for cyclophosphamide, see below for further details. • Participants ≥65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement, according to standard practice at the treating institution. • Participants <18 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement or by serum creatinine collection, according to standard practice at the treating institution. Participants <18 years of age must have GFR ≥70mL/min/1.73m^2 OR have a serum creatinine based on age/gender as follows:	

Age	Maximum serum creatinine (mg/dL)	
	Male	Female
10 to < 13 years	1.2	
13 to <16 years	1.5	1.4
16 to <18 years	1.7	1.4

Hepatic	
Total bilirubin Participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)	≤1.5 x ULN (isolated bilirubin ≤1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

System	Laboratory Value
ALT	≤2.5 x ULN (or ≤5 x ULN if documented history of liver metastases)
Coagulation[d]	
International normalized ratio (INR) OR prothrombin time (PT) / Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Nutritional status	
Albumin	≥3.5 g/dL

a. No platelet transfusions within 14 days.
b. No red blood cell transfusions to meet minimum hematologic values for eligibility.
c. Organ function will be reassessed prior to **lymphodepletion**: if, upon consultation with the Medical Monitor, there is evidence from laboratory values that recovery from last anti-cancer treatment is underway, hematology labs may be considered acceptable and requirements waved to proceed with lymphodepletion.
d. Prior to **lymphodepletion**, please refer to Section 7.5.2 for guideline on use of anticoagulant medications.

15. Participant is fit for leukapheresis and has adequate venous access for the cell collection.
16. Male or female. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or until persistence of gene modified cells in the participant's blood is below the level of detection for 2 consecutive assessments, whichever is longer.

Refrain from donating sperm

Plus, either:

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

OR

Must agree to use contraception/barrier as detailed below

- Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception described in Section 12.4 when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant (as a condom may break or leak)
- Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

b. Female Participants:

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

- Is not a WOCBP as defined in Section 12.4

  OR

- Is a WOCBP (as defined in Section 12.4) who will agree to use a barrier method (male condom) and use a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Section 12.4 during the intervention period and 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. WOCBP should also agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before any dose of study intervention.

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

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

17. Female participants of childbearing potential (FCBP) must have a negative urine or serum pregnancy test.

6.1.3 *Treatment Eligibility Screening*

In addition to confirming Treatment fitness per Section 6.1.3.1, the following criteria must also apply prior to lymphodepletion:

18. Participant has received/completed treatment with an anthracycline-containing regimen for advanced (metastatic or inoperable) disease and progressed. Participants who received neoadjuvant/adjuvant anthracycline or ifosfamide based therapy and progressed will be eligible. Participants who are intolerant to anthracycline and received ifosfamide alone unless intolerant to or ineligible to receive ifosfamide will be eligible.
19. Participant has measurable disease according to RECIST v1.1.
20. Participant has documented radiographic evidence of disease progression from prior line of therapy.
21. A biopsy (excisional, incisional, or core) of non-target tumor tissue obtained within 28 days prior to initiating lymphodepleting chemotherapy is mandatory if clinically feasible. This biopsy will be used as baseline for biomarker analyses. If it is not feasible to obtain a fresh biopsy, an archival tumor tissue (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 bridging or

standard of care intermediate anti-cancer therapy, the screening biopsy will be used for baseline.

22. A hematologist has been consulted prior to lymphodepletion in participants who have had a serious/significant bleeding/thrombosis history.

6.1.3.1 Treatment fitness (for safety)

Given potential changes in clinical status between screening/enrollment and the start of lymphodepleting chemotherapy, safety assessments from Section 6.1.1 and Section 6.1.2 will be reassessed prior to lymphodepletion. If the results of any assessments or procedure are outside of the eligibility criteria, please consult with the GSK Medical Monitor prior to proceeding with lymphodepletion.

6.2 EXCLUSION CRITERIA

6.2.1 *Target Expression Screening*

*Participants are not eligible to be screened for target expression (HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1) if any of the following criteria apply:*

1. Central nervous system (CNS) metastases.
2. Any other prior malignancy that is not in complete remission.

   Exceptions include:

   a. Completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma (e.g., melanoma in situ, basal cell carcinoma, prostate cancer in-situ, periosteal osteosarcoma)
   b. Previous malignancies that have been definitively treated, and have been in remission for 5 years may be enrolled upon consultation with sponsor Medical Monitor or designee
3. Previous treatment with genetically engineered NY-ESO-1-specific T-cells.
4. Previous NY-ESO-1 vaccine or NY-ESO-1 targeting antibody.
5. Prior gene therapy using an integrating vector.
6. Previous allogeneic hematopoietic stem cell transplant.
7. Clinically significant systemic illness:

   a. serious active infections or significant cardiac, pulmonary, hepatic or other organ dysfunction, that in the judgment of the Investigator would compromise the participant's ability to tolerate protocol therapy or significantly increase the risk of complications

   OR

   b. prior or active demyelinating disease

6.2.2 *Leukapheresis Eligibility Screening*

Participants are not eligible for leukapharesis if any of the Exclusion criteria from Section 6.2.1 apply. Please note in particular that mandatory washout period restrictions must be respected (see Table 6) before starting leukapheresis. In addition, participants are not eligible for leukapharesis if any of the following criteria apply:

8. Participant has history of chronic or recurrent (within the last year prior to leukapheresis) severe autoimmune or immune mediated disease (e.g. Crohn's disease, systemic lupus) requiring steroids or other immunosuppressive treatments.
9. Uncontrolled intercurrent illness including, but not limited to:
    a. Ongoing or active infection (including, but not limited to systemic fungal infection)
    b. Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class 3 or Class 4
    c. Uncontrolled clinically significant arrhythmia
    d. Acute coronary syndrome (angina or myocardial infarction) in last 6 months
    e. Interstitial lung disease (participants with existing pneumonitis as a result of radiation are not excluded; however, participants cannot be oxygen dependent)
10. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per Investigator assessment).

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

11. QTc >480 msec

    NOTES:

    The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.

    The specific formula that will be used to determine eligibility for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

    For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

12. Participant has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to cyclophosphamide, fludarabine, other agents used in the study.
13. Pregnant or breastfeeding females (due to risk to fetus or newborn).

14. Prior/Concomitant Therapy:
    a. Any prior treatment-related toxicities must be CTCAE (Version 5.0) Grade ≤1 at the time of initiating study intervention (except for non-clinically significant toxicities e.g., alopecia, vitiligo). Participants with Grade 2 toxicities that are deemed stable or irreversible (e.g. chemotherapy related arthritis or tendinitis, skin discoloration or erythema) can be enrolled.
    b. Other standard of care lines of therapy are allowed only if guidelines and washout periods are followed as described in Table 6.
15. Investigational treatment within 30 days or 5 half-lives (whichever is shorter) prior to leukapheresis. Investigational vaccines (other than NY-ESO-1 vaccines that are not allowed) must follow the washout period specified in Table 6. Exceptions to this rule must be evaluated by the Investigator in agreement with the Sponsor's Medical Monitor (or designee).
16. Participant has active infection with HIV, HBV, HCV, EBV, CMV, syphilis, or HTLV as defined below:
    - Positive serology for HIV;
    - Active hepatitis B infection as demonstrated by test for hepatitis B surface antigen. Participants who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation;
    - Active hepatitis C infection as demonstrated by hepatitis C RNA test. Participants who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. If HCV antibody is positive, eligibility will be determined based on a negative Screening RNA value;
    - Active EBV infection. Participants with positive EBV serology need to undergo additional tests/assessments in order to rule out active infection;
    - Active CMV infection. Participants with positive CMV serology need to undergo additional tests/assessments in order to rule out active infection;
    - Positive test for syphilis (spirochete bacterium)
    - Positive serology for HTLV 1 or 2.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

6.2.3 *Treatment Eligibility Screening*

Please note that mandatory washout period restrictions must be respected (see Table 6) before starting lymphodepletion. In addition to confirming Treatment fitness per Section 6.2.3.1, participants cannot proceed with lymphodepletion or treatment if any of the following criteria apply:

18. Participant has received cytotoxic therapy within 3 weeks prior to lymphodepleting chemotherapy.

19. Systemic corticosteroids or any other immunosuppressive therapy within 2 weeks prior to lymphodepleting chemotherapy.

    NOTE: Isolated doses of systemic corticosteroids are permitted to manage acute allergic reactions. Use of inhaled or topical steroids is not exclusionary

20. Participant has received ≥50 Gy to a significant volume of the pelvis, long bones or spine, or a cumulative dose of radiation that, in the Investigator's opinion would predispose patients to prolonged cytopenia after lymphodepletion.

21. All of the participant's measurable lesions have been irradiated within 3 months prior to lymphodepletion. An irradiated measurable lesion with unequivocal progression following irradiation may be considered a target lesion regardless of time from last radiotherapy dose.

    NOTE: There is no washout period for palliative radiation to non-target lesions

22. Participant has received an anti-cancer vaccine within 2 months in the absence of tumor response. The participant should be excluded if their disease is responding to an experimental vaccine given within 6 months.

23. Participant has received live vaccine within 4 weeks prior to lymphodepletion or intends to receive live vaccine during the 3 month period following administration of lete-cel.

24. Participant has received immune therapy (monoclonal antibody therapy, checkpoint inhibitors) within 4 weeks of lymphodepletion.

25. Participant had major surgery ≤28 days of first dose of study intervention.

Table 6 Washout Periods for Substudy 2

Treatment/Therapy[a]	**Required Washout Prior to Leukapheresis**	**Required Washout Prior to Lymphodepletion**
Cytotoxic chemotherapy	3 weeks	
Immune therapy (including monoclonal antibody therapy)	4 weeks	
Anticancer Vaccine	• 2 months in the absence of tumor response • The participant should be excluded if the Investigator considers their disease is responding to an experimental vaccine given within 6 months	
Live-virus vaccination (there is no required washout for seasonal flu vaccines that do not contain live virus).	4 weeks	
Systemic corticosteroids or any other immunosuppressive therapy (there is no washout required for inhaled or topical steroids as they are allowed during the study)	2 weeks	
Investigational treatment	4 weeks	2 weeks
Radiotherapy	To the target lesions within 3 months prior to lymphodepletion.[b] NOTE: There is no washout period for palliative radiation to non-target lesions	
Tyrosine kinase inhibitors	1 week	

a. Permission and washout for any other anticancer therapies must be discussed with the Sponsor's Medical Monitor (or designee).
b. A lesion with unequivocal progression may be considered a target lesion regardless of time from last radiotherapy dose.

6.2.3.1 Treatment fitness (for safety)

Given potential changes in clinical status between screening/enrollment and the start of lymphodepleting chemotherapy, safety assessments from Section 6.2.1 and Section 6.2.2 will be reassessed prior to lymphodepletion. If the results of any assessments or procedure are outside of the eligibility criteria, please consult with the GSK Medical Monitor prior to proceeding with lymphodepletion.

6.3 Lifestyle Considerations

6.3.1 Meals and Dietary Restrictions

Participants should maintain the current/regular diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.3.2 Activity

Participants should abstain from extraordinarily strenuous athletic activity for 24 h before each blood collection for clinical laboratory tests. Participants may engage in light recreational activities during studies (e.g., watching television, reading).

6.3.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. 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 lines of anti-cancer treatments, performance status and any serious adverse events (SAEs).

6.3.4 Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure or withdrawal) may be rescreened upon Sponsor agreement.
Rescreened participants will be assigned a new participant number.

For each rescreened participant, the Sponsor will review the following on evaluation of eligibility to Substudy 2 and before initiating leukapheresis or manufacturing of the T cells:

- Participant will be considered HLA positive if already tested positive for HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles by a validated test in a designated central lab under this substudy or under another GSK-sponsored study or substudy of this protocol;

- Participant's tumor antigen expression will be considered positive if previously pathologically reviewed by a designated central laboratory under this substudy or under another GSK-sponsored study or substudy of this protocol, with confirmed positive NY-ESO-1 expression defined as ≥30% of cells that are 2+ or 3+ by immunohistochemistry;
- If participant has previously completed Sponsor protocol-specified leukapheresis under this substudy or under another GSK-sponsored study or substudy of this protocol:
  - Already banked cryopreserved T cells under an applicable process may be used in the manufacturing of lete-cel if within shelf-life specifications;
  - Already stored manufactured lete-cel (GSK3377794) product under an applicable process may be used for the T-cell infusion if within shelf-life specifications.

7 STUDY INTERVENTION

7.1 Study Intervention(s) Administered

7.1.1 Leukapheresis

Participants will undergo leukapheresis to obtain starting material for the manufacture of autologous letetresgene autoleucel (lete-cel, GSK3377794).

Investigators will follow institutional guidelines and the minimum requirements as outlined in the Apheresis Manual.

A CD3 count of ≥200/µL prior to leukaheresis is recommended to ensure an adequate T-cell collection for manufacture of lete-cel. If the lab test returns a value lower than 200, there is the potential that more than one collection will be needed to reach the T-cell target. The lab test should be repeated and the Sponsor alerted as soon as possible.

7.1.2 Bridging Therapy and/or Standard of Care Intermediate Anti-Cancer Therapy before Lymphodepletion

Since HLA-typing and NY-ESO-1 expression testing are required prior to treatment, standard of care systemic chemotherapy, experimental therapy and/or local therapy (e.g., radio-therapy, cryoablation, surgical resection) may be administered between target expression screening and leukapheresis. Mandatory washout periods prior to leukapheresis (see Section 6.2 Table 6) must be respected when planning treatment or procedure.

Additionaly, because this substudy allows leukapheresis to occur in earlier lines of therapy, systemic chemotherapy may be administered between leukapheresis and the start of lymphodepletion (bridging therapy), if a participant has progressive disease and cannot be treatment-free. Mandatory washout periods prior to lymphodepletion (see Table 6) must be respected when planning treatment or procedure. For therapies not already described in this protocol, washout periods must be around 5 half-lives, except for biologic agents for which a Sponsor consultation is required.

At the discretion of the Investigator and after discussion with the Medical Monitor, bridging or standard of care intermediate anti-cancer therapy may be considered for any participant, particularly those with high disease burden or disease-related symptoms at screening.

Clinically significant interactions have been reported for doxorubicin with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g. verapamil) and also with inducers of CYP3A4 (e.g., phenobarbital, phenytoin, St. John's Wort), which may affect the concentration of doxorubicin, and therefore should be used with caution.

A line of standard of care therapy may be administered to participants before lymphodepletion based on Investigator's evaluation of benefit/risk, in accordance with local regulatory requirements and standards, and in agreement with the Sponsor's Medical Monitor (or designee).

7.1.3 Lymphodepleting Chemotherapy

Prior to the administration of lymphodepleting chemotherapy, participant's fitness for lymphodepletion will be assessed, treatment eligibility criteria will be confirmed and baseline tumor assessment CT/MRI obtained per Section 9.1.1 of the Core Protocol and the SoA in this Substudy. Disease progression after prior line of treatment per RECIST v1.1 needs to be documented prior to performing lymphodepletion.

When lete-cel has been manufactured, has fulfilled release criteria, and is available for infusion at the site, lymphodepleting fludarabine and cyclophosphamide can be administered as described in Table 7. Cyclophosphamide and fludarabine will be supplied by the pharmacy of the participating Institution.

Dose and regimen for lymphodepleting chemotherapy is adjusted for participants ≥60 years of age, as specified in Table 7. The investigator must discuss with the Sponsor's Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen. in situations such as but not limited to the following:

- Participants with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia),
- Participants with 3 or more prior lines of therapies,
- Participants with documented extensive prior radiation of the pelvis, long bones or spine,
- Participants with documented history of intensive chemotherapy that could reduce the bone marrow reserve,
- Participants with documented low albumin (≤3.5 g/dL).

A default dose adjustment for participants meeting one of the listed conditions should be aligned to the standard dose modification otherwise applied for participants ≥60 years of age, as specified in Table 7.

For any more complex conditions further discussion to determine the need for dose modification with the Sponsor's Medical Monitor or designee will be warranted.

For Investigators with patients approaching lymphodepletion, the Sponsor requires that the site reviews creatinine clearance (CrCl) and lymphodepleting chemotherapy dose calculations with the Medical monitor or designee. Before lymphodepletion, site must provide Sponsor with intended doses (in mg/day) of fludarabine and cyclophosphamide, patient's height, weight, gender, ethnicity, baseline serum creatinine(s) and creatinine clearance (estimated or measured). Any significant discrepancy that would lead to a change in dose will be discussed with Medical monitor prior to commencing lymphodepletion.

- Calculations methods are provided in Section 6.1 Table 5 Definitions of Adequate Organ Function, Renal for CKD-EPI using BSA (e.g. DuBois), but institutions may use their own BSA calculator (e.g Mosteller), if required per local institutional practice.
- If there is variability in pre-leukapheresis and pre-lymphodepletion serum creatinine by ±30%, institution must consider more formal/accurate measure rather than rely on estimation of creatinine clearance.

If the infusion of lete-cel is delayed > 2 weeks, in general lymphodepleting chemotherapy should be repeated. The Investigator is expected to discuss the participant's condition and the treatment plan with the Medical Monitor.

Supportive therapy guidelines are provided in Section 12.7.

Table 7 Lymphodepleting Chemotherapy

	Lymphodepleting chemotherapy					Recommended prophylaxis and supportive medication
Day	**Drug**	**Dose, mg/m²**	**Dose for participants ≥ 60 years old, mg/m²**	**Route**	**Administration[c]**	Infection: On admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Section 12.7 or in line with institutional standard practice. Hydration: Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions Mesna: May be given to prevent urotoxicity per institutional guidelines or as recommended in this Section below. G-CSF: Must start ~24 hours after the last cyclophosphamide infusion (i.e., on Day-3). G-CSF support to continue until
-7	Fludarabine[1]	30	none	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	
-6	Fludarabine[1]	30	30	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	
	Cyclophosphamideh[3]	900	600	IV	in 200 – 500 mL 0.9% NaCl over 1 hour[2]	
-5	Fludarabine[1]	30	30	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	
	Cyclophosphamide[3]	900	600	IV	in 200 – 500 mL 0.9% NaCl over 1 hour[2]	
-4	Fludarabine[1]	30	30	IV	in 50 – 100 mL 0.9% NaCl over 30 mins[2]	

	Lymphodepleting chemotherapy					Recommended prophylaxis and supportive medication
	Cyclophosphamide[3]	900	600	IV	in 200 – 500 mL 0.9% NaCl over 1 hour[2]	resolution of neutropenia in accordance with ASCO guidelines [Smith, 2015] or institutional practice.
-3	Start G-CSF[4]					
+1	Lete-cel (GSK3377794)					

1. Fludarabine dose will be adjusted in renal impairment as described in this section. This adjustment needs to be applied to all doses, on top of the age-related modification. Fludarabine dose will not be adjusted by body weight per ASBMT guidelines that recommend dosing based upon body surface area (BSA) using actual body weight [Bubalo, 2014], unless required otherwise by institutional guidelines.
2. Or per institutional guidelines.
3. Cyclophosphamide dose will be adjusted in obese participants and in pediatric participants as described in this section. This adjustment needs to be applied to all doses, on top of the age-related modification.
4. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose ~24 hours after the last chemotherapy administered.

ASCO = American Society of Clinical Oncology; ASBMT = American Society for Blood and Marrow Transplantation practice; IV = intravenous; NaCl = sodium chloride; G-CSF = granulocyte-colony stimulating factor

Fludarabine Dose Adjustment for Renal Impairment

This adjustment needs to be applied to all doses, on top of the age-related modification. The dose of fludarabine will be adjusted for participants with renal dysfunction as follows:

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

Note: to estimate CrCl (in mL/min) please use Section 6.1 Table 5 for calculation steps before comparing to the thresholds given above.
If estimating CrCl using the CKD-EPI equation, adjust the result by multiplying by (BSA/1.73) to obtain a CrCl in mL/min. For fludarabine dosing for this BSA calculation, use actual body weight.
Creatinine clearance must be reassessed prior to lymphodepletion for use in these calculations.

Cyclophosphamide Dose Adjustments

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

Calculating Ideal Body Weight

	Estimated ideal body weight (IBW) in kg
Males	$\text{IBW} = (0.9 \times \text{height in cm}) - 88$
Females	$\text{IBW} = (0.9 \times \text{height in cm}) - 92$

Estimation of Ideal Body Weight may be performed per local institutional guidelines instead.

Calculating Adjusted Body Weight

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

$$ABW = IBW + 0.4 \times (\text{actual weight} - IBW)$$

Estimation of Adujsted Body Weight may be performed per local institutional guidelines instead.

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

Cyclophosphamide Dose Adjustment for Pediatric Participants

This adjustment needs to be applied to all doses, on top of the renal impairment modification. For pediatric participants, where participant weight is >175% of the calculated IBW use the following formula to calculate cyclophosphamide dose:

$$ABW = IBW + 0.25 \times (\text{actual weight} - IBW)$$

Estimation of Adujsted Body Weight may be performed per local institutional guidelines instead.

Use ABW in the calculation for body surface area (BSA).

Mesna

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

- 50% of cyclophosphamide daily dose (450 or 300 mg/m^2) divided into 4 doses at times 0 (start of cyclophosphamide infusion) and then 3 hours, 6 hours and 9 hours after the start of each cyclophosphamide infusion.

7.1.4 Lete-cel (GSK3377794) Infusion

Refer to the current version of the Lete-cel Investigator's Brochure regarding lete-cel and related clinical experience. Refer to the Drug Product and Infusion Manual for details and instruction on storage and administration of lete-cel.

Participants will receive a single dose of lete-cel four days after completing the lymphodepleting chemotherapy. This is considered Day 1 and all procedures and assessments to be performed are listed in the SoA. Supportive care guidelines are provided in Section 12.7.

Tocilizumab availability in institution's local pharmacy

A minimum of 2 doses of tocilizumab available for each participant will be required for administration within 2 hours after T-cell infusion, if needed for treatment of Cytokine Release Syndrome (CRS).

Premedication

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

GSK3377794 Dose

The dose of GSK3377794 will be within the range of 1×10^9 – 15×10^9 transduced T cells, which will be administered by a single intravenous infusion on Day 1. The minimum transduced cell dose for meeting release criteria is 1×10^9.

If the transduced cell dose is less than the minimum dose required, manufacturing of additional transduced T cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range. In the event that no banked leukapheresis product is available, a second leukapheresis may be performed to achieve a dose in the target range.

Dosing of participants weighing less than 40 kg (including pediatric participants): For participants weighing less than 40 kg, lete-cel will be dosed per body weight with a range of 0.025×10^9 transduced cells/kg to 0.2×10^9 transduced cells/kg. The per body weight adjusted dosing can only be manufactured from the intended commercial cell manufacturing process and participants weighing less than 40 kg will only be treated with intended commercial drug product supply, as soon as it becomes available. Screening of such participants may, however, begin before intended commercial drug product supply availability.

Pediatric participants weighing greater than or equal to 40 kg will be dosed per adult dosing.

Lete-cel (GSK3377794) Administration

On Day 1, the participant will receive thawed T cells by intravenous infusion. Prior to infusion, two clinical personnel in the presence of the participant, will independently verify and confirm that the information on the infusion bag is correctly matched to the participant, as per the sponsor's and clinical site's procedures.

The specific instructions for preparation and administration are found in Drug Product and Infusion Manual.

Any deviation from the procedures detailed in the Drug Product and Infusion Manual should be recorded and reported accordingly.

In the event of adverse reaction to the cell infusion, the infusion rate should be reduced, and the reaction managed according to institutional standard procedures (Section 12.7). Steroid treatment should be avoided unless medically required. In the event a participant develops a febrile episode following the infusion, appropriate cultures and medical

management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia.

The day of T-cell infusion may be delayed in participants with significant complications of lymphodepleting chemotherapy if according to the Investigator it is in the best interest of the participant. The timing of all assessments post-infusion will be calculated with reference to the T-cell infusion date. Participants who have undergone leukapheresis but do not receive the T-cell infusion will be replaced. Cytopenias alone should not be a reason to delay T-cell infusion unless complications are present (see Section 12.7 for guidance).

Vital signs will be recorded prior to the infusion (see SoA).

7.2 Preparation / Handling / Storage / Accountability

1. Deliveries of the investigational product are correctly received by a responsible person. Deliveries are recorded.
2. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The participant's T-cell product received at the site from the manufacturer will be stored below -130°C until ordered by the Investigator (or designee) to be infused.
5. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of unused study intervention will be provided in the Study Reference Manual or Drug Product and Infusion Manual.

Precaution will be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the Investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable to this open-label substudy.

7.4 Study Intervention Compliance

Lete-cel will be intravenously administered to participants at the site per guidelines specified in the Drug Product and Infusion Manual.

Administration will be documented in the source documents and reported in the eCRF.

7.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving starting at the time of screening for leukapheresis or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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

1. All prescription and non-prescription medication, vitamins, herbal and nutritional supplements taken by the participant during the 30 days prior to Screening for leukapheresis will be recorded at the Screening Phase visit.
2. All prior anti-cancer treatments taken by the participant must be recorded regardless of time.
3. All concomitant medications taken by the participant while in the Interventional Phase.
4. Use of any mutagenic agents or investigational agents must be reported.
5. Concomitant medications administered after the Interventional phase of the study will be recorded for SAEs and adverse events of special interest (AESIs).

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

7.5.1 Prohibited Concomitant Medication and Treatment

The following anti-cancer treatments are prohibited during the Interventional Phase of the study until PD is confirmed: non-protocol chemotherapy, immune therapy, biological therapy (including targeted therapies with tyrosine kinase inhibitors or monoclonal antibodies), or investigational anti-cancer therapy. Once PD has been confirmed following T-cell infusion, participants can receive therapy at the discretion of their healthcare provider while they remain in this study. This includes participation in other interventional clinical studies as needed.

During the Interventional Phase of the study until PD is confirmed participants should also not undergo other anticancer locoregional therapies, such as surgical resection, excisional biopsies or non-palliative radiation. Procedures intended for palliative care or symptomatic relieve on non-target lesions are permitted.

Systemic steroids may abrogate the effects of the T cell therapy and therefore are discouraged unless required to manage CRS (refer to Section 12.7 for CRS management) or other significant immune-mediated AEs. According to local standard of care or American Society of Clinical Oncology (ASCO) guidelines [Basch, 2010], steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the investigational product. Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

Systemic glucocorticoids are prohibited for any purpose other than to treat an event of suspected immunologic etiology (see Section 12.7). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants may receive other medications that the Investigator deems to be medically necessary in agreement with the Sponsor's Medical Monitor (or designee).

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Administration of live vaccine during the period of infusion of fludarabine, cyclophosphamide or lete-cel, and for at least 3 months after last dose of any of these agents is prohibited. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the Investigator, the Sponsor and the participant.

7.5.2 Permitted Concomitant Medication and Treatment

Participants should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

Lesions that previously required radiotherapy should be recorded prior to lymphodepleting chemotherapy. Radiotherapy is not permitted after T-cell infusion until disease progression. However, in emergent clinical situations, palliative radiation for pain relief to non-measurable lesions or non-target lesions present at baseline may be permitted upon approval of Sponsor's Medical Monitor. However, lesions requiring radiotherapy after the T-cell infusion should be evaluated as to whether that indicates disease progression. These lesions are not suitable to be biopsied for biomarker analysis.

Other treatment that the Investigator considers necessary for a participant's welfare may be administered during the Interventional Phase of the study at the discretion of the Investigator in keeping with community standards of medical care and in adherence to the protocol. Before immunizing a participant at high risk for vaccine-preventable disease

(or member of the participant's household), consult an Infectious Disease specialist or a guidance such as the CDC Clinical Practice Guideline for Vaccination of the Immunocompromised Host.

Permitted concomitant medications with required washout periods are listed in Section 6.2, Table 6 of this Substudy.

Once PD has been confirmed following T-cell infusion, participants can receive further therapy at the discretion of their healthcare provider while they continue to be followed in this study.

Recommendations for participants on therapeutic anticoagulants: [Maus, 2020]

- Before proceeding with lymphodepletion, participants on therapeutic anticoagulants should be switched from long-acting to short-acting formulations, wherever possible. Long-acting anticoagulants can significantly potentiate bleeding risk during CRS.
- If platelet counts drop below 100,000/µL in participants undergoing study treatment, dual-acting anticoagulants should be discontinued.
- If platelet counts drop below 50,000/µL in participants undergoing study treatment, all anticoagulants should be discontinued unless a patient has a recent thrombosis.
- If platelet counts drop below 50,000/µL in participants undergoing study treatment and the patient has a recent thrombosis, anticoagulants may be continued, but the dose should be reduced or platelet transfusions should be administered.

7.5.3 Rescue Medicine

Anti IL-6 drugs such as Tocilizumab may be administered to participants experiencing cytokine release syndrome (see Section 12.7.5 for details). Steroids may be used for emergent medical conditions. For all non-emergent conditions, consult with the Sponsor's Medical Monitor. Guidelines for management of complications are provided separately in the appendices.

See Section 12.7 for details on general supportive care that can be given during the study.

7.6 Dose Modification

Dose modification is not applicable to T cells. The entire dose of T cells that has been received by the site for the participant needs to be administered as a single dose. If a reaction occurs that does not allow safe administration of the full dose, the dose administered needs to be recorded.

If the transduced cell dose is less than the minimum dose required, manufacturing of additional transduced T cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range. In the event that no banked leukapheresis product is available, a second leukapheresis may be performed to achieve a dose in the target range.

7.7 Intervention after the End of the Study

No therapeutic intervention will be provided after the end of the study. Participant may receive any necessary treatment interventions from their oncologist.

8 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

Definitions and procedures for discontinuation of study intervention and participant discontinuation / withdrawal should follow the SoA in this substudy and details outlined in Core Protocol Section 8.

9 STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures should be performed per the SoA in this substudy and as defined in the Core Protocol Section 9.

The following additional Substudy specific assessments should be performed per the SoA.

9.1 Interviews

9.1.1 Post T-cell Infusion Interview

To evaluate T-cell infusion related experiences, symptoms and associated impacts, adult participants will be asked to participate in an optional telephone interview. Adult participants will be contacted about one week after infusion to set up a phone interview. The informed consent for this phone interview will be part of the clinical trial informed consent process. All of the interviews will be conducted by a trained interviewer will be audio recorded for transcription and analysis. Failure to complete the interviews will not constitute a protocol deviation.

9.1.2 End of Treatment Interview

To further evaluate disease and treatment related symptoms and associated impacts on function and health-related quality-of-life, adult participants will complete an optional Exit Interview conducted via telephone within approximately 21 days following completion of the last Interventional Phase visit and will focus on symptoms and impacts following discontinuation of study intervention. Failure to complete the interviews will not constitute a protocol deviation.

9.2 Patient Reported Outcomes

Patient reported outcomes will be assessed in adult participants as part of this protocol. The instruments in use in this section are only suitable for adult populations.

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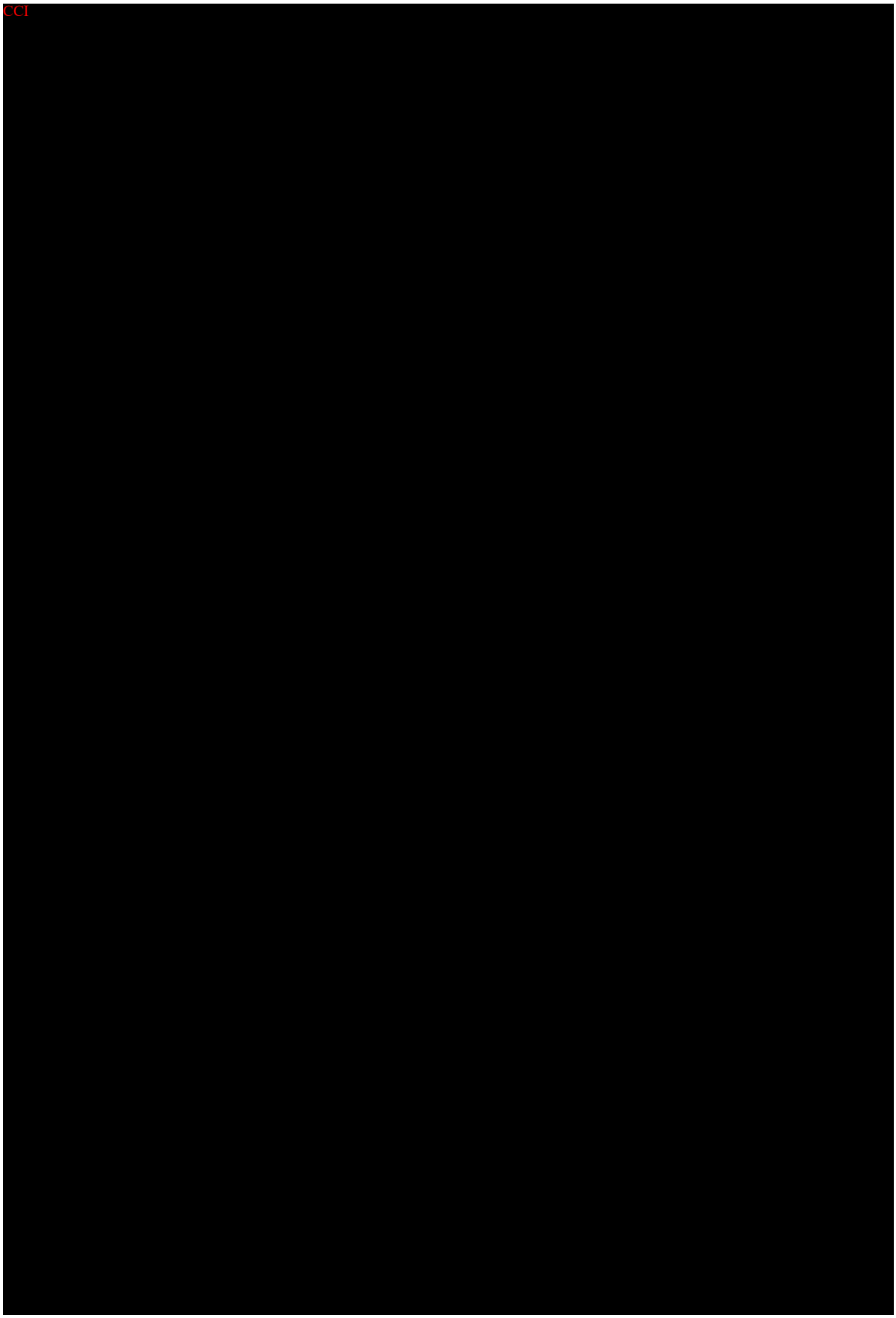

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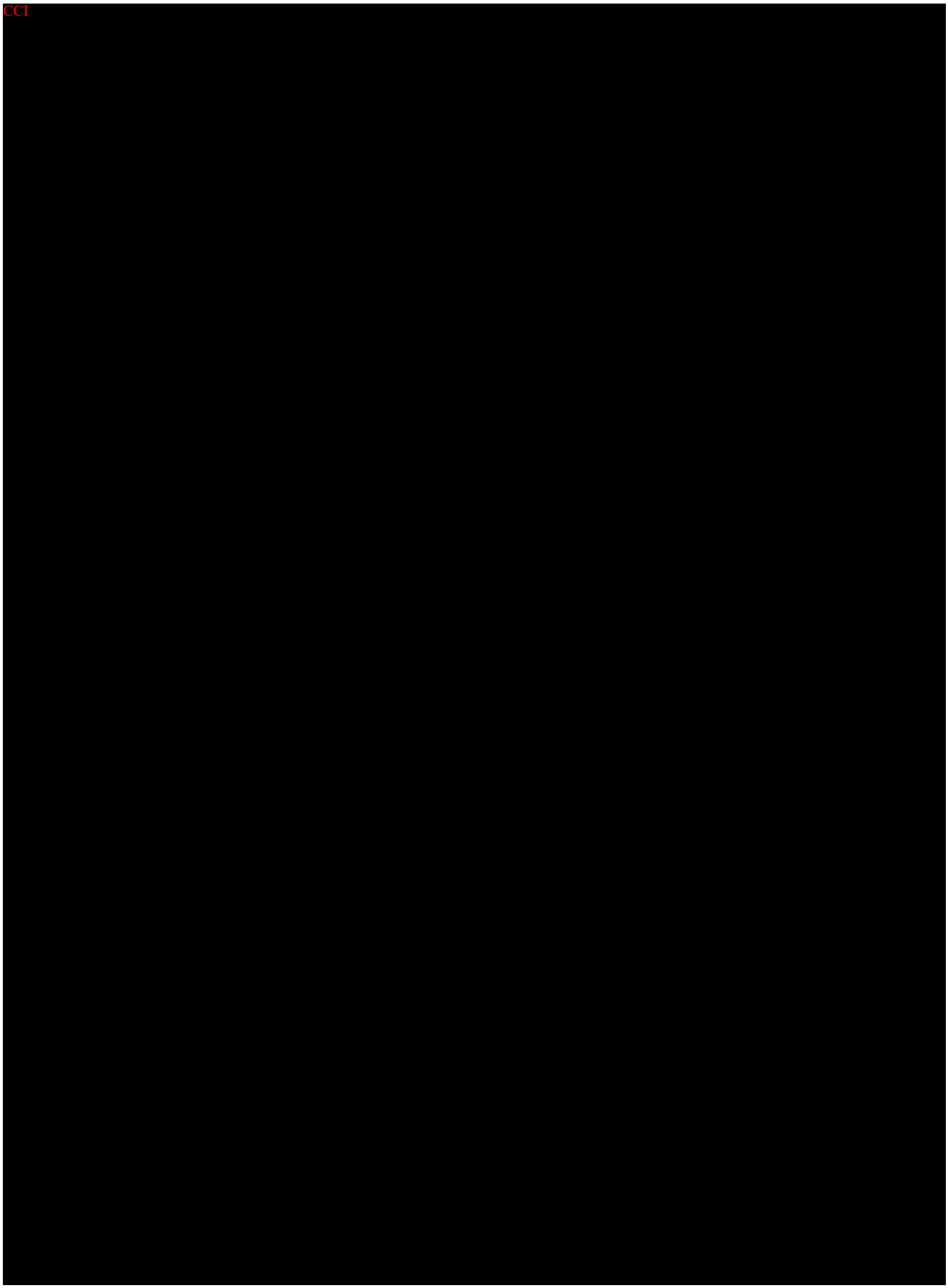

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9.3 Healthcare Resource Utilization

Healthcare resource utilization (HRU) is to be collected per the Schedule of Activities (SoA). The site staff will complete the paper Healthcare Utilization Worksheet using information available from the electronic medical records (EMR) and participant interview. The site staff will enter the data from the Healthcare Utilization Worksheet into the eCRF.

All oncology related HRU since the last visit will be collected, including the current visit.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

This substudy is designed to evaluate the benefit/risk of lete-cel relative to historical controls. The ORR for pazopanib and other available second line (2L) treatments ranges between 4-13% based on available data. To account for the potential variability in historical control efficacy, the upper range of the historical ORR of 13% is considered. It is expected that treatment with lete-cel will result in a 40% ORR or higher.

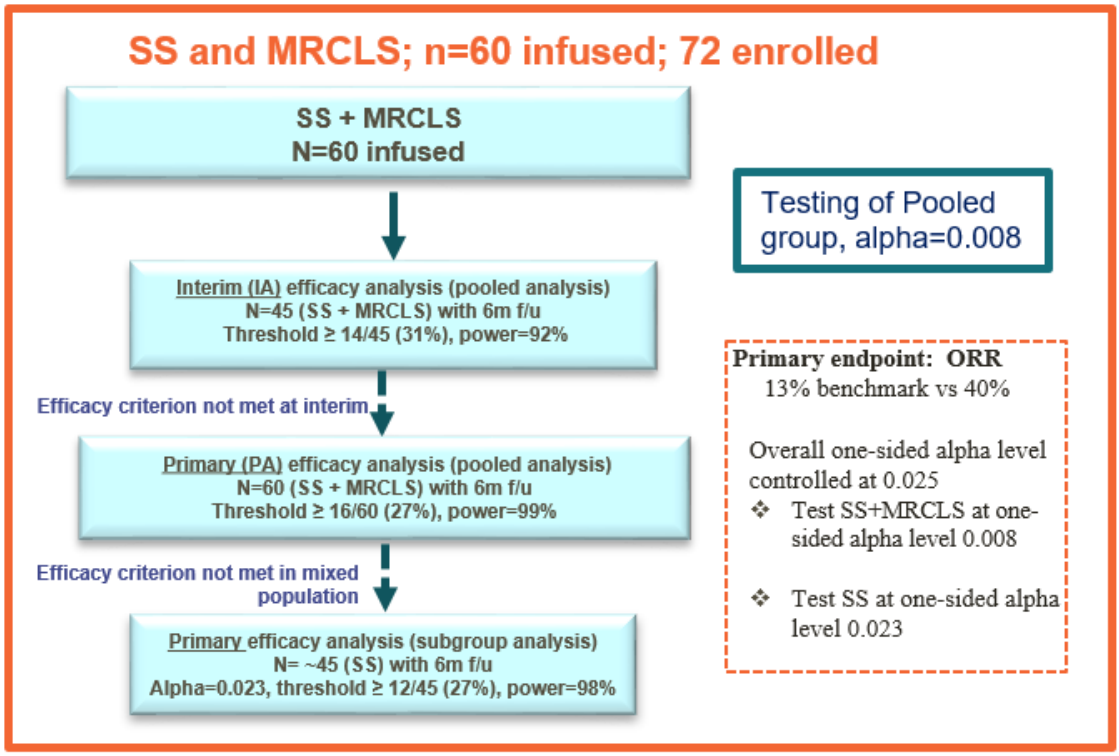
The primary efficacy analysis will be performed by testing whether the ORR is less than or equal to 13% against the alternative hypothesis that ORR is greater than 13% at overall 2.5% level of significance (one-sided), that is H0: $p \leq 0.13$ vs. H1: $p > 0.13$. The ORR will be summarized along with the two-sided exact Clopper-Pearson 95% confidence interval (CI). The study will be considered successful if the lower bound of the two-sided exact confidence interval for ORR exceeds 13%. The primary analysis will be based on the combined data from both SS and MRCLS. Additional subgroup analyses by indication may be prepared as appropriate.

A hierarchical testing strategy is being implemented which will maintain an overall alpha-level of 0.025 for assessing ORR across the study as described below - further details included in the Analysis Plan:

- **Interim Analysis 1:** After approximately 20 patients have been infused with intended commercial drug product supply lete-cel and followed for approximately 3 months, an interim analysis will be conducted to facilitate planning and discussion with relevant health authorities regarding further development and registration strategy for lete-cel. No early claim for efficacy is planned and no alpha adjustment is planned for this analysis.
- **Interim Analysis 2:** After 45 patients have been infused with intended commercial drug product supply lete-cel and followed for approximately 6 months, efficacy will be evaluated for the overall population (SS+MRCLS). Observing an ORR of 14 of 45 responders would provide a successful outcome for the study.
- **Primary Efficacy Analysis:** After 60 patients have been infused with intended commercial drug product supply lete-cel and followed for approximately 6 months,

efficacy will be evaluated for the overall population (SS+MRCLS). Observing an ORR of 16 of 60 responders would provide a successful outcome for the study.

- **Primary Efficacy Analysis (SS sub-population):** After 60 patients (SS+MRCLS) have been infused with intended commercial drug product supply lete-cel and followed for approximately 6 months, the SS sub-population will be evaluated. Observing an ORR of 12 of 45 responders would provide a successful outcome for the study.



Overall one-sided alpha level controlled at 0.025
α_1 for pooled analyses (SS+MRCLS), which is divided between α_{IA} and α_{PA} = 0.008 (Song & Chi et. al 2007)
α_2 for subgroup SS analysis = 0.023 (Wang et. al 2007)

10.2 Sample Size Justification

Based on the exact binomial distribution and the null hypothesis of ORR ≤13% and alternative hypothesis of ORR >13%, a sample size of 60 participants in the PEAP population will provide over 98% power to demonstrate statistical significance at one-sided 0.025 type 1 error rate, if the underlying ORR is 40%. In this setting, an ORR of 26.6% (16/60) will be needed to claim success at the time of primary analysis with the two-sided exact Clopper-Pearson 95% confidence interval (CI). The study will be considered successful if the lower bound of the two-sided exact confidence interval for ORR exceeds 13%.

Though a smaller sample size could be utilized for the efficacy assessment with adequate power >90%, the larger sample size has been implemented to allow for a more robust evaluation of safety.

The primary analysis will be performed after the first 60 participants have received T-cell infusion (PEAP population) and have completed at least 6-months of follow-up since infusion or progressed or discontinued earlier (due to death, loss to follow-up, or permanent study withdrawal). The final analysis will be performed when 70% of the total number of participants who received at least the minimum target dose of lete-cel (mITT) have died or have been lost to follow-up.

The PEAP sample size proposed for Study 208467 (N=60) is sufficient to demonstrate the risk / benefit in this highly selected and rare patient population. It is assumed that approximately 5%-10% of enrolled participants will not receive lete-cel infusion due to consent withdrawal, product manufacturing issues, death occurring before progression on prior lines of treatments, being ineligible to receive lete-cel after progression, or other issues. Approximately 72 participants will be enrolled to ensure that at least 60 participants are treated with intended commercial drug product supply.

At the time of the primary analysis (n=60 participants), it is anticipated approximately 45 SS participants and 15 MRCLS participants will be treated. The distribution between SS and MRCLS participants treated may naturally vary from the projections. A summary of the sample size sensitivity for the SS subgroup analysis is also provided to show the power under different scenarios if the sample size for the SS subgroup is less than the planned n=45 SS patients.

N for SS/pooled	Alpha for SS analysis	Power for SS analysis
45/60	0.02285	98%
43/60	0.0223	98%
40/60	0.0219	97%
35/60	0.0211	94%

10.3 Populations for Analyses

For purposes of analysis, the following populations are defined, the details of additional analysis populations will be defined in RAP:

Population	Description
Screened Population	All participants who signed an ICF to participate in the study.
Enrolled Population	All participants who started leukapheresis procedure.
ITT Population	All participants who started leukapheresis procedure.

Population	Description
Safety Population	All participants who received any dose of lete-cel (GSK3377794).
Modified ITT (mITT) Population	All participants who received at least the minimum target dose[1] and meeting the product specifications[2] of lete-cel.
Primary Efficacy Analysis Population (PEAP)	The first 60 participants who received at least the minimum target dose[1] and meeting the product specifications[2] of lete-cel from intended commercial drug product supply. This population will be the primary population for the primary/secondary efficacy analysis.
Primary Efficacy Analysis Population for Interim (PEAPi)	The first 45 participants who received at least the minimum target dose[1] and meeting the product specifications[2] of lete-cel from intended commercial drug product supply. This population will be the primary population for the primary/secondary efficacy interim analysis.

1. Minimum target dose = $1x10^9$ transduced cells of lete-cel.
   Note: while all manufactured products are to be released with a dose greater than the minimum target dose, it may be possible that a participant does not receive the intented minimum target dose, due to an AE requiring infusion discontinuation, or due to a bag being quarantined.
2. Participants who received drug product supply released as "non-conforming batch" will be excluded from mITT, PEAP and PEAPi populations.

The primary efficacy analysis population (PEAP) will be used for the primary analysis (n=60). The PEAPi will be used in place of the PEAP at the time of the interim analysis (n=45) for the planned analyses.

A summary of the number of participants in each of the analysis populations will be provided. A listing of participants excluded from analysis populations (if any) will also be provided.

A summary and listing of screening status and screen failures will be provided using the screened population.

10.4 Study Population Analyses

The study population analyses will be based on the ITT, mITT and PEAP population, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, exposure and treatment compliance will be based on GSK Core and Oncology Data Standards.

Disposition of Participants

The number of participants receiving lymphodepleting chemotherapy and the number of participants infused with the minimum target dose of 1×10^9 transduced cells of lete-cel will be summarized. A summary of participant status, reason for study withdrawal and

study treatment status will be provided. This display will show the number and percentage of participants who completed the study, those withdrew from the study, those ongoing for study.

Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be summarised and listed.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

Demographic and Baseline Characteristics

The demographic characteristics (e.g., race, age, ethnicity, sex, height, and baseline body weight) will be summarized and listed. Age, height, weight will be summarized using the mean, standard deviation, minimum, median and maximum. In addition, age will also be categorized and summarized by GSK IDSL standard as ≤18, 19-64, ≥65. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized and listed.

Concomitant Medication

All concomitant medications will be summarized.

Concomitant medications will be coded using WHO Drug coding dictionary, summarized and listed. The summary of concomitant medications will show the number and percentage of participants taking concomitant medication by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxycillin on two separate occasions, the participant is counted only once under the ingredient ‘Amoxycillin’. In the summary of concomitant medications, the ingredients will be summarized by the base only.

Blood products will be summarized. Supporting listing will also be provided.

Study Treatment Exposure

A listing of study treatment will be provided, including participant number, total cells, transduction efficiency, derived total transduced dose, and lot number / T-cell manufacturer. The total number of transduced T cells will be summarized using mean, standard deviation, median and range.

All dose administration data for lymphodepletion, including cyclophosphamide and fludarabine, for T-cell infusion will be presented by participant in a data listing.

Subsequent Anti-Cancer Therapies

The number and percentage of participants that received any anti-cancer medication, radiotherapy or cancer-specific surgery as post study treatment anti-cancer therapy will be summarized. Time from T-cell infusion to the first post study treatment anti-cancer therapy will also be included in this summary table.

Follow-up anti-cancer therapy will be coded using WHO Drug coding dictionary, then summarized by ingredient. Participant level details of the anti-cancer therapy will be provided in the listings. On-study surgeries and radiotherapy will be listed.

10.5 Statistical Analyses

10.5.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	ORR, which includes confirmed complete or partial response as determined by independent review assessment will be reported along with Clopper-Pearson exact 95% CI.
Secondary	PFS, OS, DOR, and TTR will be summarized using Kaplan-Meier quantile estimates along with 2-sided 95% CIs at the time of final analysis, if data warrant. DCR will be reported along with Clopper-Pearson exact 95% CI.
Exploratory	Will be described in the reporting and analysis plan.

Primary Efficacy Analysis

ORR: Overall response rate is defined as the percentage of participants with a confirmed CR or a PR relative to the total number of participants within the analysis population per RECIST v1.1 as determined by central independent review. At the primary analysis, ORR will be analysed based on the PEAP population.

ORR will also be reported in the ITT and mITT populations at the time of primary analysis for all participants who have had at least two post-baseline disease assessments or have died or progressed or have withdrawn from the study. Additional sensitivity analysis will be performed using the ORR as assessed by local Investigators at final analysis.

The overall response is the overall response recorded from the start of T-cell infusion until disease progression or start of new anti-cancer therapy, whichever earlier, and will be determined programmatically based on disease assessment at each time point.

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 at the primary analysis along with 95% Clopper-Pearson exact CI.

An overall listing of participant response data will be provided for the ITT population. This listing will be sorted by the first T-cell infusion date and will display all the central independent review response evaluations, the best confirmed response, whether the participant is ongoing in the study, whether the participant is evaluable for the PEAP population. All supporting lesion data will be listed.

Secondary Efficacy Analysis

DCR: DCR, is defined as the percentage of participants with a confirmed CR, PR, or SD with minimal 12 weeks duration relative to the total number of participants within the analysis population at the time of primary analysis as determined by independent central review per RECIST v1.1. The observed DCR will be reported along with 95% Clopper-Pearson exact confidence interval (CI). DCR will be analysed based on PEAP and mITT populations.

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 outlined in RECIST v1.1, will be listed and summarized separately, as appropriate.

PFS: PFS, is defined as the time from the date of T-cell infusion until the earliest date of radiological PD as assessed by independent central review per RECIST v1.1, or death due to any cause. For the analysis of PFS, if the participant received subsequent anticancer therapy prior to the date of documented events, PFS will be censored at the last adequate disease assessment (e.g., assessment when visit level response was CR, PR, or SD) prior to the initiation of the new anticancer therapy. If a participant does not have an adequate post-baseline disease assessment that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of the T-cell infusion date.

Since missing scheduled radiological disease assessments prior to radiological progression or death increases the uncertainty when the event actually occurs, PFS will be censored for participants who have radiological progression or die after missing more than two scheduled radiological disease assessments. Specifically, if there are more than two scheduled radiological assessments which are missing followed by radiological progression or death, PFS will be censored at the last adequate radiological assessment prior to radiological progression or death. If a participant does not have an adequate post-baseline disease assessment prior to the date of radiological progression or death, PFS will be censored at the date of the T-cell infusion date.

If a participant has neither progressed, died, nor started new anti-cancer therapy, PFS will be censored at the date of the last adequate disease assessment.

For participants who receive subsequent anti-cancer therapy the following rules will apply:

- If anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, PFS will be censored at the date of the last adequate disease assessment that is no later than the date of initiation of anti-cancer therapy (i.e., if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used, as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy).
- If a participant has only a baseline visit or does not have an adequate disease assessment that is no later than the date of initiation of subsequent anti-cancer therapy, PFS will be censored at the date of T-cell infusion.

A summary of the assignments for progression and censoring dates for PFS are specified in table below.

Situation	**Date of Event (Progression/Death) or Censored**	**Event (Progression/Death) Or Censored**
No (or inadequate) baseline tumor assessments and the participant has not died (if the participant has died follow the rules for death indicted at the bottom of the table)	Date of T-cell infusion	Censored
No post-baseline adequate disease assessments and the participant has not died (if the participant has died follow the rules for death indicted at the bottom of the table)	Date of T-cell infusion	Censored
Progression documented between scheduled visits	Date of assessment of progression [1,3]	Event
No progression (or death)	Date of last adequate disease assessment of response [2]	Censored
New anticancer treatment started (prior to documented disease progression) [3]	Date of last adequate disease assessment of response [2] (on or prior to starting anti-cancer therapy)	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after more than two missed adequate disease assessment	Date of last adequate disease assessment of response [2] (prior to missed assessments)	Censored

1. The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).
2. An adequate disease assessment is defined as an assessment where the response is CR, PR, or SD. For purposes of defining adequate assessment, PD is not considered adequate.

3. If PD and new anti-cancer therapy (including systemic ctx, radiotherapy and cancer-related procedures) occur on the same day, assume the progression was documented first (e.g. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of T-cell infusion.

PFS will be listed and summarized using Kaplan-Meier quartile estimates along with 2-sided 95% CIs.

OS: OS, is defined as the interval of time between the date of T-cell infusion and the date of death due to any cause. For participants who do not die, time of death will be censored at the date of last contact. The date of death should be taken from that recorded on the Record of Death page. Death on study due to any cause will be included. Survival will be listed and summarized using Kaplan-Meier quartile estimates along with 2-sided 95% CI.

DOR: DOR is defined as, in the subset of participants who show a confirmed CR or PR as assessed by independent central review per RECIST v1.1, 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. Censoring: same as PFS censorship table.

TTR: TTR is defined as the time from the date of T-cell infusion to initial date of confirmed response (PR or CR) as assessed by independent central review per RECIST v1.1 in the subset of participants who achieved a confirmed PR or CR.

TTR will be listed and summarized descriptively using median and quartiles in the subset of participants with a confirmed response of PR or CR.

Efficacy listings such as BOR , DOR, PFS and OS will be reported for the PEAP and mITT populations.

Sensitivity Analysis

The analysis of primary endpoint, ORR, will also be performed among all participants in the ITT population.

Additional sensitivity analysis will be performed for the ORR, PFS and DOR as assessed by local Investigators.

Specifically, the ORR based on local Investigators assessed response will be determined programmatically and summarized in the same way as the ORR based on independent central review. An assessment of the concordance between the Investigator-assessed response and independent central review assessed response will be performed. An overall listing of participants response data based on Investigator assessed response will be provided alongside the independent central review assessed responses for the mITT population. This listing will be sorted by by the first T-cell infusion date and will display both independent reviewer-assessed and Investigator assessed response evaluations, the best confirmed responses, whether the participant is ongoing in the study, and whether the participant is evaluable for the PEAP.

The sensitivity analysis of PFS and DOR will be based on radiological response from the local Investigator assessment. The date of disease progression is defined as the date of radiological disease progression based on imaging data per RECIST v1.1. Participants who do not meet the RECIST v1.1 criteria for progression and are still alive will be censored. Clinical progression, defined as Investigator assessed clinical progression in the absence of radiological confirmation, is not considered a progression event in this analysis. Specifically, in the event of clinical progression leading to discontinuation of study treatment and radiological assessment, if radiological assessments do not indicate radiological progression, then the participant will be censored at the time of last radiological assessment. If a participant has not progressed, not died, and not started new anti-cancer therapy, PFS and DOR will be censored at the date of the last adequate assessment. Censoring rule for the sensitivity analysis of PFS and DOR will be the same as the censoring rule for the secondary efficacy analysis for PFS as described above.

As a sensitivity analysis, PFS and DOR based on local Investigator assessment will be summarized and listed similarly as that of PFS and DOR based on independent reviewer assessment.

10.5.2 Safety Analyses

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

Endpoint	Statistical Analysis Methods
Primary	AEs will be summarized using frequencies and proportions.
Secondary	AEs/SAEs/AESIs will be summarized using frequencies and proportions; RCL and instances of insertional oncogenesis (IO) will be summarized descriptively.
Exploratory	Will be described in the reporting and analysis plan

Safety data will be presented in tabular and/or graphical format and summarized descriptively. In the case of low-event count, listings may be provided in lieu of summaries.

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, if warranted, and across all on-treatment time points using a “worst-case” analysis. Complete details of the safety analyses will be provided in the RAP.

Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class (SOC) and preferred term (PT). The severity of AEs will be graded by the Investigator according to the NCI-CTCAE v5.0. In addition CRS and ICANS will be graded according to [Lee, 2019].

PT may be combined and reported together as one term. The combined terms for MedDRA will be included/updated in the RAP. For all tables that summarize AEs by just PT, the combined version of the terms will be used. Tables that summarize AEs by SOC and PT will use the explicit MedDRA preferred terms.

Events will be summarized by frequency and proportion of total participants and by SOC and PT. Separate summaries will be given for all AEs, treatment-related AEs, treatment-related SAEs, SAEs, AESIs, 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. AEs will be sorted by PT in descending order of total incidence.

A summary of non-serious AEs that occurred in 5% of the participants or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g. events with 4.9% incidence rate should not be included in this table). This summary will contain the number and percentage of participants with common non-serious adverse events. The summary table will be displayed by SOC and PT.

Summaries will be provided for lymphodepletion-related and T-cell infusion-related adverse events separately by overall frequency and maximum grade. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. The summary tables by maximum grade will be displayed in descending order of total incidence by PT only.

All AEs will be listed. The relationship between MedDRA SOC, PT, and Verbatim Text will be displayed in a listing. Additionally, a listing of participant IDs for each individual AE will be produced.

Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

According to Section 9.4.7 of protocol, AESIs for this trial include, but are not limited to:

- Cytokine release syndrome (CRS)
- Graft vs host disease (GvHD)
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grade 1 persisting beyond 24 hrs or associated with concurrent CRS; or Grade 2 or higher
- Guillain Barré syndrome (GBS) including acute inflammatory demyelinating polyneuropathy (AIDP)
- Pancytopenia/aplastic anemia
- Treatment-related inflammatory response at tumor site(s)

For each AESI category, time from T-cell infusion to first onset (in days) and duration of first occurrence will be summarized.

The number and percentage of participants with these events will be summarized by categories of AESI and maximum grade in one table.

Listing for participants experiencing AE of GvHD will be provided, which will include leukapheresis date, chemo start date, T-cell infusion date, AE start date, time since infusion (days), AE end date, severity, relationship to the lymphodepleting chemotherapy, relationship to T cell infusion outcome of event.

Listing for participants experiencing AESI of CRS will also include time from infusion to first CRS (days) and time from infusion to max CRS (days).

AEs of special interest will be further outlined in the RAP.

Deaths and Serious Adverse Events

In the event that a participant has withdrawn consent, no data after the withdrawal of consent date from this participant (except publically available information such as date of death) is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarized based on the number and percentage of participants. This summary will classify participants by time of death relative to the date of T-cell infusion (>30 days or ≤30 days) and primary cause of death. A supportive listing will be generated to provide participant-specific details on participants who died.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. One summary will be displayed by SOC and PT. Another table will summarize the frequency and percentage of SAEs in descending order of total incidence by PT only.

Summaries will be provided for lymphodepletion-related and T-cell infusion-related SAEs separately by overall frequency and maximum grade. A summary will also be provided for fatal adverse events, as well as separate summaries for study treatment-related fatal SAEs, as described above.

SAEs are included in the listing of all adverse events. Separate supportive listings with participant-level details will be generated for

- Fatal SAEs
- Non-fatal SAEs.

Clinical Laboratory Evaluations

Summary of post-baseline change of laboratory values by visit will be provided.

Summaries of worst case grade increase from baseline grade will be provided for all the laboratory tests that are gradable by CTCAE. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Missing baseline grade will be assumed as Grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

For laboratory tests that are not gradable by CTCAE, summaries of worst case changes from baseline with respect to normal range will be generated. The worst case will be

chosen from all available tests, including scheduled and unscheduled visits. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Separate summary tables for haematology, chemistry, urinalysis and laboratory tests will be produced.

A supporting listing of laboratory data for participants with any value outside normal range will be provided, as well as laboratory values and urinalysis values.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of participants with non-missing value at each particular visit.

Further details on the analysis of exploratory endpoints and the list of statistical analysis displays will be provided in the RAP.

Replication Competent Lentivirus (RCL) and instances of insertional oncogenesis (IO)

RCL and instances of IO will be summarized descriptively.

10.5.3 Immunogenicity

Presence and titres of anti-lete-cel antibodies over time will be summarized based on Safety population.

10.5.4 Other Analyses

PK, pharmacodynamic, and biomarker analyses will be described in the RAP.

10.5.5 Interim Analyses

Interim Analysis 1: An interim analysis is included to facilitate planning and discussion with relevant health authorities regarding further development and registration strategy for lete-cel. The interim analysis will occur after approximately 20 participants have been treated with intended commercial drug product supply and followed up for approximately 3 months. No early claim of efficacy is planned at the Interim Analysis 1, and no alpha adjustment is planned for this analysis. Data from approximately 10 additional patients treated with clinical supply will also be provided for review. This interim analysis will use efficacy data based on Investigators' assessments instead of the independent central review assessments.

Interim Analysis 2: A formal interim analysis is planned when 45 patients have been treated with intended commercial drug product supply and followed up for approximately 6 months. The primary endpoint of ORR based on independent central review data will be assessed for the combined group (SS+MRCLS).

Interim safety data will be provided to the IDMC on a regular basis. Interim efficacy data will be provided at the pre-specified interim efficacy analyses. Details will be specified in the IDMC charter.

14 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.

14.1 Amendment 1 (21-JUN-2019)

Overall Rationale for Amendment 1:

The overall rationale for this amendment is addition or clarification of aspects related to participant safety and rationale for Substudy 1 patient population. These additions included modification of lymphodepleting regimen for older participants, and changes related to FDA requests including addition of study stopping rules, and update to both the Encephalopathy (now Immune Effector Cell-Associated Neurotoxicity or ICANS) and the CRS grading and management criteria.

Section # and Name	Description of Change	Brief Rationale
Core protocol		
8 Discontinuation of study intervention	Section added: 8.5 Study stopping and pausing rules	FDA request
9.3.2 Physical examinations	Added developmental assessments for pediatric participants	To monitor long-term effects of study treatment on participant development
9.3.3 ECOG and Appendix 8 ECOG	Added Lansky and Karnofsky assessment scales for pediatric participants	To align with other protocols across the GSK3377794 program
9.4 Adverse events and serious adverse events	Added delayed AE definition. Modified AE and SAE collection times for the study; added clarification to AEs collected during follow-up post disease progression to match SoA	To align with other protocols across the GSK3377794 program and to improve protocol clarity
12.7.5 Management of CRS	Revised guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system	FDA request
12.7.8 Management of encephalopathy	Revised guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system [Lee, 2019]	FDA request
Substudy 1		
1 Synopsis and 5 Study design	Study schemas modified to include adjustments for lymphodepletion regimen	To improve participant safety

Section # and Name	Description of Change	Brief Rationale
2. Schedule of activities	Added developmental assessments for pediatric participants; added Lansky and Karnofsky assessments; modified AE and SAE collection times; added ePRO collection at Week 3	To monitor long-term effects of study treatment on participant development: ePRO changes to evaluate short-term impacts of treatment and adverse events on quality of life between Week 1 and Week 6.
3.1 Background and rationale and 3.2 Benefit/risk assessment	Revised rationale and benefit/risk conclusions for inclusion of participants with previously untreated advanced synovial sarcoma	FDA request
6.1 Inclusion criteria	Added Lansky and Karnofsky scales to assessing performance status in pediatric participants	To align with other protocols across the GSK3377794 program
7.1.3 Lymphodepleting chemotherapy	Added lymphodepleting regimen adjustments for participants ≥ 60 years old and participants with severe cytopenia	To improve participants safety
Substudy 2		
1 Synopsis and 5 Study design	Study schemas modified to include adjustments for lymphodepletion regimen	To improve participant safety
2 Schedule of activities	Added developmental assessments for pediatric participants; added Lansky and Karnofsky assessments; modified AE and SAE collection times; added ePRO collection at Week 3	To monitor long-term effects of study treatment on participant development: ePRO changes to evaluate short-term impacts of treatment and adverse events on quality of life between week 1 and week 6.
5 Study design	Allow Substudy 2 screening to begin prior to the availability of the commercial vector supply and cell manufacturing process	To align with the original intent to allow participant screening on Substudy 2 prior to availability of the commercial vector supply and cell manufacturing process
6.1 Inclusion criteria	Added Lansky and Karnofsky scales to assessing performance status in pediatric participants	To align with other protocols across the GSK3377794 program
7.1.3 Lymphodepleting chemotherapy	Added lymphodepleting regimen adjustments for participants ≥ 60 years old and participants with severe cytopenia	To improve participants safety
10.5.1 Efficacy Analyses	Corrected the inconsistency in ORR analysis language to align with primary analysis language in Section 10.2.	FDA request
Throughout		
	Corrected inconsistencies and typos	To improve quality of the protocol

14.2 Amendment 2 (05-FEB-2020)

Overall Rationale for Amendment 2:

The primary rationale for protocol Amendment 2 is clarification of aspects related to drug product supply used for treatment on Substudy 2.

Per protocol Amendment 1, for Substudy 2, at least 45 participants will be treated using the intended commercial vector supply and cell manufacturing processes (application supplement to be submitted). In the event participants eligible for Substudy 2 require treatment before commercial drug product supply is available, protocol Amendment 2 allows for treatment to begin with the currently registered drug product supply. Such participants, if any, will be replaced to ensure that at least 45 participants receive the intended commercial drug product supply.

An additional rationale for protocol Amendment 2 is clarification of dosing regimen and drug product supply used for treatment of participants weighing less than 40 kg on Substudies 1 and 2. This protocol Amendment 2 implements an updated dose range per body weight for participants weighing less than 40 kg as per the Investigator's Brochure version 11 update [GlaxoSmithKline Document Number 2018N369930_03, 2019]. Clarification is also provided that participants weighing less than 40 kg will only be treated with the intended commercial cell manufacturing process, and that screening of such participants may begin before commercial drug product supply is available.

Section # and Name	Description of Change	Brief Rationale
Core protocol and throughout document		
	Updated Investigator's Brochure version from 10 to 11	To update reference
Substudy 1		
7.1.4 GSK3377794 Infusion GSK3377794 Dose Pediatric Dosing	Maximum of target dose range for participants weighing less than 40 kg amended from 0.125 to $0.2x10^9$ transduced cells/kg. Participants weighing less than 40 kg will only be treated with the intended commercial drug product supply.	To match with IB version 11 update To clarify that GSK3377794 dosing per body weight for participants weighing less than 40 kg can only be provided from the commercial cell manufacturing process
Substudy 2		
3.1 Substudy 2 Background and Rationale 5.1 Overall design 5.2 Number of participants	Updated language to allow for Substudy 2 to start treatment eligible participants with currently registered drug product supply while restating the intent to dose at least 45 participants with commercial drug product supply.	To start enrolling while ensuring that no delay could prevent first participants from receiving treatment in a timely manner.
7.1.4 GSK3377794 Infusion GSK3377794 Dose Pediatric Dosing	Maximum of target dose range for participants weighing less than 40 kg amended from 0.125 to $0.2x10^9$ transduced cells/kg. Participants weighing less than 40 kg will only be treated with the intended commercial drug product supply.	To match with IB version 11 update To clarify that GSK3377794 dosing per body weight for participants weighing less than 40 kg can only be provided from the commercial cell manufacturing process
10.2 Sample size justification 10.3 Populations for Analyses	An additional modified Intent-To-Treat population (mITTc) is defined as a subset of the already existing mITT, to only include participants who received GSK3377794 infusion from commercial drug product supply. Primary Efficacy Analysis Population (PEAP) is also redefined to only include the first 45 participants who received GSK3377794 infusion from commercial drug product supply. PEAP used for sample size justifications instead of mITT	To allow for separate analyses of all participants dosed with GSK3377794 (mITT) versus all participants dosed with GSK3377794 commercial drug product supply (mITTc) To ensure that the PEAP is only considering participants dosed with commercial drug product supply

14.3 Amendment 3 (06-APR-2020)

Overall Rationale for Amendment 3:

The primary rationale for protocol Amendment 3 is to address regulatory agency's requests and integrate protocol clarification letters that were issued to date.

Protocol amendment 3 addresses feedback from regulatory agencies by defining an end of study for the Master Protocol, by clarifying the hospitalization and monitoring requirements for T-cell infusion, and by clearly defining contraception requirements.

Protocol amendment 3 also further clarifies schedule of assessments, washout periods prior to leukapheresis and prior to lymphodepletion for Substudy 1 and 2, requirement for availability of tocilizumab and treatment/management of pediatric participants. Further data collection for all screened subjects, assessment of TGF-β levels have been added.

Protocol amendment 3 also updates eligibility criteria that participants from Substudies 1 and 2 who are enrolled under clinical drug product supply need to weigh ≥40 kg. Conditions for rescreening of participants who have failed screening or withdrawn have been clarified such that, for patients who have previously completed protocol-specified target expression testing and/or leukapheresis, the Sponsor will confirm the eligibility and use of any cryopreserved leukapheresis and/or manufactured product on evaluation for an applicable substudy.

Section # and Name	Description of Change	Brief Rationale
Core protocol		
1. Synopsis 3.1 Study rationale	Clarified that c259 is the specific retained clone from the TCR optimization, and that it is also called NY-ESO-1^{c259}.	To clarify language
1. Synopsis 5.1 Overall Design	Clarified hospitalization instructions from T-cell infusion (on Day 1) and close monitoring requirements until Day 14.	To clarify patient safety monitoring in response to regulatory agency's request.
1. Synopsis 6.2 Rescreening (new)	Clarified conditions for rescreening participants in the same or a different substudy.	To clarify evaluation of rescreened participants and to reduce repetition of specific tests/procedures.
1. Synopsis 5.1 Overall Design 12.7.9.1 Management of Neutropenia	Clarified and aligned wording relating to initiation of G-CSF on Day -3.	To clarify initiation of G-CSFsupport.
3.1 Study Rationale 3.3 GSK3377794	Relocated last paragraph of section to Section 3.3. Removed table of Clinical studies.	To clarify background/IP sections and improve readability of document
5.1 Overall Design	Added that cryopreserved T-cell product from leukapheresis has a shelf-life of 2 years. Clarified language for obtention of the pre-treatment tumor biopsy if not feasible to obtain fresh biopsy.	To clarify language. To address site feedback and clarify acceptance and window for obtention of baseline biopsy.
5.3 End of Master Protocol Definition	Section 5.3,Section 5.3.1 and Section 5.3.2.added to clarify End of Study for Individual Participants and End of the Master Protocol.	To clarify End of Study and End of Master Protocol in response to regulatory agency's request.
6.1 Screen failure	Added collection of disease characteristics, prior lines of anti-cancer treatment and performance status for all participants at target expression screening visit.	To clarify that collection of medical history, prior anti-cancer line of treatment and performance status are required for screen failure participants.

Section # and Name	Description of Change	Brief Rationale
6.2 Rescreening (new)	Specifed that rescreened participants will be assigned a new participant number. For participants who have previously completed protocol-specified target expression testing and/or leukapheresis, the Sponsor will confirm the eligibility and use of any cryopreserved leukapheresis and/or manufactured product on evaluation for an applicable substudy.	To implement new participant number assignment for any rescreening. To clarify elibility for rescreened participants.
9.2 Patient Reported Outcomes	Clarified that patient reported outcome instruments in use for Substudies 1 and 2 are only validated for adult populations.	To clarify that patient reported outcomes in Substudies 1 and 2 are only required for adult participants.
9.3.4 Vital signs	Clarified that blood pressure, pulse measurements, respiratory rate, and body temperature should be assessed per institutional standards.	To clarify requirements on vital signs assessments.
9.3.9 Monitoring and Management of Replication-Competent Lentivirus (RCL) using Vesicular Stomatitis Virus G protein (VSV-G) 9.3.10 Testing for Persistence of Transduced T cells and Insertional Oncogenesis	Theoretical risks for RCL and Insertional Oncogenesis requalified as potential risk.	To harmonize with safety risk denomination.
9.4 Adverse Events and Serious Adverse Events	Updated definition for delayed adverse events as occurring either after disease progression or last Interventional Phase visit, whichever occurs first.	To amend definition of delayed adverse events per updated FDA 2020a guidance.
9.4.5 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.	To specify contraception requirements, in response to regulatory feedback.

Section # and Name	Description of Change	Brief Rationale
9.9.3 Cytokine Analyses 12.7.5 Management of Cytokine Release Syndrome	Clarified that if cytokine release syndrome (CRS) is suspected, serum for cytokine analysis should be collected every day for the first week and approximately every other day thereafter until symptoms improve or an alternative diagnosis is confirmed.	To specify cytokine collection requirements in case of suspected CRS.
9.9.8 Stool Collection for Microbiome Analysis (new)	Added plans to analyse gut microbiome.	To specify planned analysis of collected stool samples.
12.3.4 Recording of Follow-Up of AE and SAE – Assessment of Intensity	Clarified that CRS grading will be conducted according to [Lee, 2019]	To clarify assessment of AE and SAE intensity of CRS.
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.
12.7.2.2 Herpex Simplex and Varicella Zoster 12.7.2.4 Hepatitis B prophylaxis	Clarified that prophylaxis for herpex simplex and varicella zoster should be initiated prior to lymphodepletion. Clarified that posology provided for prophylaxis regimen is for adult participants (refer to label or institutional guidelines for posology on paediatrics).	To clarify prophylaxis language.
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.

Section # and Name	Description of Change	Brief Rationale
Substudy 1		
2. Schedule of Activities (SoA)	Clarified that patient reported outcome in use for Substudies 1 and 2 are only required for adult participants. Specified when triplicate ECGs are required. Clarified instructions on timing of Blood Pressure (BP) assessments, cytokine collection and pre-treatment biopsy. Combined sampling for persistence and RCL testing. Added anlysis of TGF-β in plasma sample. Added collection of stool sample at baseline visit and close to Week 6 visit in order	To clarify instructions on study assessments.
2.0 SOA – Table 3 5.1 Overall Design – Part 3 6.1 Inclusion criteria 18	Clarified language for obtention of the pre-treatment tumor biopsy if not feasible to obtain fresh biopsy.	To address site feedback and clarify acceptance and window for obtention of baseline biopsy.
3.2.1 Risk Assessment GSK3377794	Theoretical risks for ICANS, RCL and Insertional Oncogenesis requalified as potential risk	To harmonize with safety risk denomination.
6.1 Inclusion criterion 2	Addition of weight requirement to be ≥40 kg for any participant enrolled under clinical drug product supply. Clarification of requirement for creatinine clearance / GFR / serum creatinine on pediatric patients.	To optimize participant safety with current dosing and formulation requirements. To clarify that pediatric patients with renal impairment are excluded.
6.1 Inclusion criterion 7	Amended text to clarify that biopsy sample should be available (instead of is) to perform NY-ESO-1 antigen expression analysis.	To clarify that both tests may occur either in parallel or sequentially, pending availability of tumor biopsy sample for NY-ESO-1 antigen expression testing.
6.1 Inclusion criteria – Leukapheresis Lymphodepletion and Treatment	Clarified that Inclusion criteria 1-7 must apply again prior to leukapheresis eligibility screening Clarified that Inclusion criteria 1-15 must apply again prior to lymphodepletion eligibility screening	To clarify instructions for leukapheresis eligibility. To clarify instructions for lymphodepletion eligibility.

Section # and Name	Description of Change	Brief Rationale
6.1 Inclusion criterion 12 Table 4 Renal	Amended inclusion criteria for adequate renal organ function: - Clarified GFR formula - Additional criteria for pediatric patients, based on GFR or serum creatinine	To clarify inclusion criterion for adequate renal organ function.
6.2 Exclusion criterion 23 7.5.1 Prohibited Concomitant Medication and Treatments	Exclusion of participants who intend to receive live vaccine during the 3 month period following administration of GSK3377794. Administration of live vaccine during the period of infusion of fludarabine, cyclophosphamide or GSK3377794, and for at least three months after last dose of any of these agents is prohibited.	To clarify exclusion criteria related to live vaccines, and prohibition of live vaccine administration during and after the period of infusion of lymphodepleting chemotherapy or GSK3377794, in response to regulatory agency's request.
6.2 Exclusion criteria – Table 5 Washout Periods for Substudy 1	Clarification for washout periods for eligibility prior to leukapheresis and prior to lymphodepletion.	To clarify that washout periods are also followed prior to leukapheresis.
6.3.3 Screen Failures	Amended to specify that rescreened participants will be assigned a new participant number. Added collection of disease characteristics, prior lines of anti-cancer treatment and performance status for all participants at target expression screening visit.	To specify that a new participant number will be assigned for any rescreening. To clarify that collection of medical history, prior anti-cancer line of treatment and performance status are required for screen failure participants.
6.3.4 Rescreening	For participants who have previously completed protocol-specified target expression testing and/or leukapheresis, the Sponsor will confirm the eligibility and use of any cryopreserved leukapheresis and/or manufactured product on evaluation for Substudy 1.	To clarify elibility for rescreened participants.
7.1.2 Supportive Therapy and/or Standard of Care Line of Therapy before Lymphodepletion	Specified that CYP3A4, CYP2D6 and/or P-glycoprotein (P-gp) inducers or inhibitors should only be used with caution when administered with doxorubicin. Clarified that use of doxorubicin in Substudy 1 is based on Investigator's judgement in accordance with label and local institutional guidances	To clarify potential drug-drug interactions with doxorubicin, in response to regulatory agency's request.

Section # and Name	Description of Change	Brief Rationale
7.1.3 Lymphodepleting Chemotherapy	Clarified that Ideal Body Weight (IBW) and Adjusted Body Weight (ABW) may be calculated according to local institutional guidances. Clarified and harmonized wording about initiation of G-CSF on Day -3. Optimized language on dose adjustement as fludarabine dosing is only adjusted based on age and renal impairment considerations. Similarly cyclophosphamide dosing is only adjusted based on age and weight considerations.	To clarify that provided formula for IBW and ABW are suggested and that local institutional guidelines are acceptable in assessment of adjustments to body surface area. To clarify instructions for lymphodepleting dose adjustments and timing of G-CSF support.
7.1.4 GSK3377794 Infusion	Corrected time between end of lymphodepletion and T-cell infusion to be four (4) days instead of two (2). Added that a minimum of 2 doses of tocilizumab must be available for each participant for administration within 2 hours after T-cell infusion if needed for treatment of CRS.	To align protocol language with rest of document. To include requirement for availability of tocilizumab.
9.2 Patient Reported Outcomes	Clarified that patient reported outcome instruments in use for Substudies 1 and 2 are only validated for adult populations.	To clarify that patient reported outcomes in Substudies 1 and 2 are only required for adult participants.
10.2 Sample size justification – Population analysis	Clarified that the Enrolled population is “All participants who passed all screening criteria for leukapheresis”	To clarify description of enrolled population.

Section # and Name	Description of Change	Brief Rationale
Substudy 2		
2. Schedule of Activities	Clarified that patient reported outcome in use for Substudies 1 and 2 are only required for adult participants. Specified when triplicate ECGs are required. Clarified instructions on timing of Blood Pressure (BP) assessments, cytokine collection and pre-treatment biopsy. Combined sampling for persistence and RCL testing. Added anlysis of TGF-β in plasma sample. Added collection of stool sample at baseline visit and close to Week 6 visit in order	To clarify instructions on study assessments.
2.0 SOA – Table 3 5.1 Overall Design – Part 3 6.1 Inclusion criteria 20	Clarified language for obtention of the pre-treatment tumor biopsy if not feasible to obtain fresh biopsy.	To address site feedback and clarify acceptance and window for obtention of baseline biopsy.
3.2.1 Risk Assessment GSK3377794	Theoretical risks for ICANS, RCL and Insertional Oncogenesis requalified as potential risk	To harmonize with safety risk denomination.
6.1 Inclusion criterion 2	Addition of weight requirement to be ≥40 kg for any participant enrolled under clinical drug product supply. Clarification of requirement for creatinine clearance / GFR / serum creatinine on pediatric patients.	To optimize participant safety with current dosing and formulation requirements. To clarify that pediatric patients with renal impairment are excluded.
6.1 Inclusion criterion 7	Amended text to clarify that biopsy sample should be available (instead of is) to perform NY-ESO-1 antigen expression analysis.	To clarify that both tests may occur either in parallel or sequentially, pending availability of tumor biopsy sample for NY-ESO-1 antigen expression testing.
6.1 Inclusion criteria – Leukapheresis Lymphodepletion and Treatment	Clarified that Inclusion criteria 1-7 must apply again prior to leukapheresis eligibility screening Clarified that Inclusion criteria 1-15 must apply again prior to lymphodepletion eligibility screening	To clarify instructions for leukapheresis eligibility. To clarify instructions for lymphodepletion eligibility.

Section # and Name	Description of Change	Brief Rationale
6.1 Inclusion criterion 12 Table 5 Renal	Amended inclusion criteria for adequate renal organ function: - Clarified GFR formula - Additional criteria for pediatric patients, based on GFR or serum creatinine	To clarify inclusion criterion for adequate renal organ function.
6.2 Exclusion criterion 22 7.5.1 Prohibited Concomitant Medication and Treatments	Exclusion of participants who intend to receive live vaccine during the 3 month period following administration of GSK3377794. Administration of live vaccine during the period of infusion of fludarabine, cyclophosphamide or GSK3377794, and for at least three months after last dose of any of these agents is prohibited.	To clarify exclusion criteria related to live vaccines, and prohibition of live vaccine administration during and after the period of infusion of lymphodepleting chemotherapy or GSK3377794, in response to regulatory agency's request.
6.2 Exclusion criteria – Table 6 Washout Periods for Substudy 2	Clarification for washout periods for eligibility prior to leukapheresis and prior to lymphodepletion.	To clarify that washout periods are also followed prior to leukapheresis.
6.3.3 Screen Failures	Amended to specify that rescreened participants will be assigned a new participant number. Added collection of disease characteristics, prior lines of anti-cancer treatment and performance status for all participants at target expression screening visit.	To specify that a new participant number will be assigned for any rescreening. To clarify that collection of medical history, prior anti-cancer line of treatment and performance status are required for screen failure participants.
6.3.4 Rescreening	For participants who have previously completed protocol-specified target expression testing and/or leukapheresis, the Sponsor will confirm the eligibility and use of any cryopreserved leukapheresis and/or manufactured product on evaluation for Substudy 1.	To clarify elibility for rescreened participants.
7.1.2 Supportive Therapy and/or Standard of Care Line of Therapy before Lymphodepletion	Specified that CYP3A4, CYP2D6 and/or P-glycoprotein (P-gp) inducers or inhibitors should only be used with caution when administered with doxorubicin.	To clarify potential drug-drug interactions with doxorubicin, in response to regulatory agency's request.

Section # and Name	Description of Change	Brief Rationale
7.1.3 Lymphodepleting Chemotherapy	Clarified that Ideal Body Weight (IBW) and Adjusted Body Weight (ABW) may be calculated according to local institutional guidances. Clarified and harmonized wording about initiation of G-CSF on Day -3. Optimized language on dose adjustement as fludarabine dosing is only adjusted based on age and renal impairment considerations. Similarly cyclophosphamide dosing is only adjusted based on age and weight considerations.	To clarify that provided formula for IBW and ABW are suggested and that local institutional guidelines are acceptable in assessment of adjustments to body surface area. To clarify instructions for lymphodepleting dose adjustments and timing of G-CSF support.
7.1.4 GSK3377794 Infusion	Corrected time between end of lymphodepletion and T-cell infusion to be four (4) days instead of two (2). Added that a minimum of 2 doses of tocilizumab must be available for each participant for administration within 2 hours after T-cell infusion if needed for treatment of CRS.	To align protocol language wording with rest of document. To include requirement for availability of tocilizumab.
9.2 Patient Reported Outcomes	Clarified that patient reported outcome instruments in use for Substudies 1 and 2 are only validated for adult populations.	To clarify that patient reported outcomes in Substudies 1 and 2 are only required for adult participants.
10.3 Populations for Analyses	Clarified that the Enrolled population is “All participants who passed all screening criteria for leukapheresis”	To clarify description of enrolled population.
Throughout the document		
	Minor edits	To improve the quality of the protocol
	FDA 2020a and FDA 2020b	To update references to new 2020 FDA guidelines for LTFU and RCL monitoring

14.4 Amendment 4 (03-DEC-2020)

Overall Rationale for Amendment 4:

The primary rationale for protocol Amendment 4 is to:

1. Include Myxoid/Round Cell Liposarcoma (MRCLS) as a second translation-related sarcoma indication to Substudies 1 and 2.

2. Allow fresh biopsies for NY-ESO-1 antigen expression screening,

3. Allow for participants with high-risk locally advanced disease to be screened on Substudy 1,

4. Amend analysis population definitions to align with program definitions.

Section # and Name	Description of Change	Brief Rationale
Core protocol		
1. Synopsis 3. Introduction 5. Study Design 6. Protocol population 9.9 Biomarkers 11. References	"Myxoid/round cell liposarcoma" included as second translocation-related sarcoma indication for Substudies 1 and 2.	Substudy 1 and 2 populations will now include HLA-A*02+ participants with NY ESO1+ advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.
1. Synopsis 4. Objectives and Endpoints	Reformatted Secondary Objectves and Enpoints into "Secondary – Efficacy", "Secondary – Safety" and "Secondary – Pharmacokinetics". Removed Overall Survival (OS) from Core secondary objectives	To clarify subcategories of secondary objectives. OS is a secondary objective for Substudy 2, but only an exploratory objective for Substudy 1.
1. Synopsis 5. Design	Study Design schematic updated to include "Myxoid/round cell liposarcoma" in Substudies 1 and 2 Total expected number of participants updated to approximately 80 for both substudies 1 and 2, and to approximately 70 for substudy 2 to account for additional 15 participants expected to be dosed with clinical drug product supply. Includes provision for allowing target expression screening, leukapheresis and manufacture to be conducted under separate GSK-sponsored protocol or substudy.	Substudy 1 and 2 populations will now include HLA-A*02+ participants with NY ESO1+ advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma. While sample sizes for key study deliverables (10 for Subtsudy 1 and approximately 55 for Substudy 2) do not change, the overall numbers must account for the expected 15 additional participants to be dosed with clinical drug product supply before the switch to commercial drug product supply is complete. Will facilitate pre-screening, and considerations for re-allocation of participants onto other suited protocols when available.
1. Synopsis 5. Design	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
5.1 Overall Design	Provides more detailed Participant Journey Screening for Substudy 1 may now start at any time after diagnosis of high risk locally advanced disease (i.e. deeply seated, high grade, positive margins, large [^{3}5 cm], or locally recurrent) 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. Initiation of leukapheresis procedure now constitutes enrollment in the study.	To clarify steps and align with the schematics Self-explanatory to allow for earlier screening of participants under Substudy 1 Clarifies that preference for target expression is sequential (HLA-typing then antigen expression) but that parallel testing is allowed. This update to the definition is aligned with that to the substudy analysis populations.
5.1 Overall Design 6. Protocol population	Allows for on-study fresh biopsies to be used for NY-ESO-1 antigen expression screening. If a fresh biopsy is obtained at screening and participant did not receive any supportive anticancer therapy, the same sample can be used for baseline.	Allows for participants who have exhausted any representative tumor specimen to undergo biopsy collection on-study.
8.1 Discontinuation of Study Intervention	Optimized wording with references to relevant sections for dose administration, safety assessment and reporting, supportive care guidance on T-cell infusion and AEs of Special interests such as Cytokine Release Syndrome (CRS).	Clarification of references.
8.2.1 Temporary Discontinuation	Clarified wording for liver toxicities during infusion with proper reference to section 8.1.	Clarification
9.3.1.1 Mandated Study Pause Due to GBS	Section removed because redundant with Section 8.5.	Removed redundancy.
9. Study Assessments and Procedures 9.3.4 Vital Signs	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.
9.4 Adverse Events and Serious Adverse Events	Updated definition of Delayed AEs to align with updated FDA guidance [FDA, 2020a].	Updated definitions of 6 categories of delayed AEs per FDA.

Section # and Name	Description of Change	Brief Rationale
9.4.5 Pregnancy	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.
9.4.6 Cardiovascular Events and Death 12.3.1 Definition of AE 12.3.2 Definition of SAE	All details for deaths including those attributed to progression of malignant disease will be reported. Any untoward medical occurrence even linked to progression of malignant disease will be reported, including SAEs, and SAEs that resulted in death.	Clarified that SAEs that are linked to progression of malignant disease should be reported.
9.8 Genetics 9.9 Biomarkers	Removed duplications between Gentetics and Biomarker sections	Optimized wording
9.9 Biomarkers	Updated requirement for the on-study biopsy originally scheduled at Week 6, to be performed at Week 4 instead, with an extended period of collection (from Week 4 until Week6)	Optimization of timing for collection, as some tumors may have already shrunk too much by Week 6.
9.9.1 Tumor Biopsy	Added requirements for on-study tumor biopsies	Clarification.
9.9.2 Liquid Biopsies	Added wording for analysis plan	Clarification.
9.9.9 Genetic Blood Sample (section added)	Section added	Added clarification on genetic analysis plan

Section # and Name	Description of Change	Brief Rationale
Substudy 1		
Substudy 1 Title Substudy 1 Subtitle	Titles and subtitles amended	To include generic drugname "Letetresgene Autoleucel" and shortname "Lete-cel" To include additional indication of "Myxoid/round cell liposarcoma"
1. Synopsis 3. Introduction 4. Objectives and Endpoints 5. Study Design 6. Study population 10. Statistical considerations	"Myxoid/round cell liposarcoma" included as second translocation-related advanced (metastatic or unresectable) sarcoma indication for Substudy 1.	Substudy 1 population will now include HLA-A*02+ participants with NY ESO1+ advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.
1. Synopsis 5. Design	Study Design schematic updated to include "Myxoid/round cell liposarcoma" in Substudy 1	Substudy 1 population will now include HLA-A*02+ participants with NY ESO1+ advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.
2. Schedule of Assessment Table 1	Corrected reference in footnote #1. Footnote #4 has been clarified with a window for collection of optional Genetic Sample (from signature of screening consent until leukapheresis procedure). Footnote#8 clarifies that 7 days must be counted from the day of leukapheresis for the window of assessments. Footnote#9 has been added to specify that the second CD3 count should be preferably performed within 24 hours from leukapheresis procedure.	Optimization of instructions.

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Assessment Table 2	Clarified that 1 month = 4 weeks on this calendar. Provided formula to clarify that Week N for N≥1 is to be scheduled on the 1st day of the week, that is on Day 7N-6 Renamed Inclusion/Exclusion for treatment to "Treatment Fitness and Inclusion/Exclusion for Treatment Eligibility" CCI [redacted]	Optimization of instructions.
2. Schedule of Assessment Table 3	Moved requirement for Week 6 on-study biopsy to Week 4 and added footnote #8 to allow for window of collection to be extended from Week 4 to Week 6 (from Day 21 to Day 39) Clarified in footnote#2 that PK, immunogenicity and Biomarker samples will not be collected at Week 10.	Optimization of instructions.
3.1 Substudy 1 Background and Rationale for First Line Therapy with GSK3377794	Updated background, added MRCLS section.	
3.2.1 Risk Assessment	Updated safety profile of GSK3377794 based on IB v12.	Update.
4. Objectives and Endpoints	Reformatted Secondary Objectves and Enpoints into "Secondary – Efficacy", "Secondary – Safety" and "Secondary – Pharmacokinetics". CCI [redacted]	To clarify subcategories of secondary objectives. To allow tools to assess MRCLS participants Optimized wording.

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	Clarified that Drug product supply type ('clinical' vs 'commercial') will be recorded in the CRF as part of the route of synthesis.	To allow for subgroup analyses between clinical and commercial supply.
5.1 Overall Design	Provides more detailed Participant Journey Screening for Substudy 1 may now start at any time after diagnosis of high risk locally advanced disease (i.e. deeply seated, high grade, positive margins, large [⩾5 cm], or locally recurrent) 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. Includes provision for allowing target expression screening, leukapheresis and manufacture to be conducted under separate GSK-sponsored protocol or substudy.	To clarify steps and align with the schematics Self-explanatory to allow for earlier screening of participants under Substudy 1 Clarifies that preference for target expression is sequential (HLA-typing then antigen expression) but that parallel testing is allowed. Will facilitate pre-screening, and considerations for re-allocation of participants onto other suited protocols when available.
5.1 Overall Design 6.1 Inclusion Criteria 6.2 Exclusion Criteria	Allows for on-study fresh biopsies to be used for NY-ESO-1 antigen expression screening. If a fresh biopsy is obtained at screening and participant did not receive any supportive anticancer therapy, the same sample can be used for baseline. Optimization of Treatment Fitness and Eligibility criteria prior to Lymphodepletion	Allows for participants who have exhausted any representative tumor specimen to undergo biopsy collection on-study. 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.
5.2 Number of participants	Clarified wording without any change to sample size	Optimization

6.1 Inclusion criteria	Amended inclusion #2 to include requirement to consult with Medical Monitor if participant is weighing <40kg and is scheduled to receive commercial drug supply.	Addition to ensure safety oversight in treatment of participants weighing <40kg.
	Amended Inclusion#3 to include translocation-specific requirements for MRCLS	Addition
	Amended Inclusion criteria #4 to allow for participants with high-risk locally advanced disease to be screened.	Allowing participants with earlier diagnosis to be screened on Substudy 1.
	Amended Inclusion #7 to allow for on-study fresh biopsy specimen for screening, and inclusion of reference to guidance on acceptable specimen in Section 5.1	Allows for fresh biopsies on study.
	Added Inclusion #8 to ensure life expectancy at leukapheresis is ≥24 weeks	
	Added Inclusion #9 to require diagnosis of advanced (metastatic or unresectable) disease prior to leukapheresis.	New addition to ensure participant survival from screening to T-cell infusion.
	Amended Inclusions #10 and #11 (formerly #8 and #9) to allow for HLA-typing and NY-ESO-1 antigen expression test to be conducted under separate GSK-sponsored protocol or substudy.	Ensure that participants candidates for leukapheresis have been diagnosed with advanced (metastatic or unresectable) disease.
	Amended Inclusion #12 (formerly #10) to exclude any evidence of clinically significant pericardial effusion.	Will allow for easier pre-screening or transfer of participants between GSK-sponsored protocols.
	Amended Table 4 of Definitions of Adequate Organ Function: - to specify ANC must be measured without G-CSF support) - to remove requirement for CD3 count - to clarify Lymphocyte count is absolute (ALC) - to clarify steps to assess creatinine clearance for participants between 18 and 65 - to add a nutritional status criterion with Albumin (≥3.5 g/dL)	Added safety precautions. Added clarity and safety precautions.
	Amended Inclusion #20 (formerly #18) to specify that fresh biopsy obtained at screening may be used at baseline if participant did not receive any supportive anti-cancer therapy in between.	

Section # and Name	Description of Change	Brief Rationale
		Added provision to only collect one fresh biopsy between screening and baseline visit if no supportive anti-cancer therapy was given in between.
7.1.3 Lymphodepleting Chemotherapy	Clarified situations where Medical Monitor must e 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	Added safety oversight and precautions. Added clarification.
9.2.2 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire	Title amended to Item Library 31 (Disease Symptoms)	Title amended per EORTC recommendation.
9.2.7 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire	Title amended to Item Library 30 (Sensory Symptoms)	Added to allow for MRCLS participants.
10.2 Sample size justification	Added that considerations will look at the pooled overall response rate (ORR) across both synovial sarcoma and myxoid/round cell liposarcoma populations. Populations for analysis: - 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” - Safety and modified Intent-To-Treat (mITT) populations were amended to the same definition of “All participants who received any dose of GSK3377794”	Optimization and standardization of reporting across the program.

Section # and Name	Description of Change	Brief Rationale
Substudy 2		
Substudy 2 Title Substudy 2 Subtitle	Titles and subtitles amended	To include generic drugname "Letetresgene Autoleucel" and shortname "Lete-cel" To include additional indication of "Myxoid/round cell liposarcoma"
1. Synopsis 3. Introduction 4. Objectives and Endpoints 5. Study Design 6. Study population 10. Statistical considerations	"Myxoid/round cell liposarcoma" included as second translocation-related sarcoma indication for Substudy 2.	Substudy 2 population will now include HLA-A*02+ participants with NY ESO1+ advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma.
1. Synopsis 5. Design	Study Design schematic updated to include "Myxoid/round cell liposarcoma" in Substudy 2 Footnote under schematic clarifies that Substudy 2 will accrue about approximately 70 participants to account for additional 15 participants expected to be dosed with clinical drug product supply.	Substudy 2 population will now include HLA-A*02+ participants with NY ESO1+ advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma. While the sample size for the key deliverables on Substudy 2 of approximately 55 does not change, the overall numbers must account for the expected 15 additional participants to be dosed with clinical drug product supply before the switch to commercial drug product supply is complete.
2. Schedule of Assessment Table 1	Corrected reference in footnote #1. Footnote #4 has been clarified with a window for collection of optional Genetic Sample (from signature of screening consent until leukapheresis procedure). Footnote#8 clarifies that 7 days must be counted from the day of leukapheresis for the window of assessments. Footnote#9 has been added to specify that the second CD3 count should be preferably performed within 24 hours from leukapheresis procedure.	Optimization of instructions.

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Assessment Table 2	Clarified that 1 month = 4 weeks on this calendar. Provided formula to clarify that Week N for N≥1 is to be scheduled on the 1st day of the week, that is on Day 7N-6 Renamed Inclusion/Exclusion for treatment to "Treatment Fitness and Inclusion/Exclusion for Treatment Eligibility" CCI [redacted]	Optimization of instructions.
2. Schedule of Assessment Table 3	Moved requirement for Week 6 on-study biopsy to Week 4 and added footnote #8 to allow for window of collection to be extended from Week 4 to Week 6 (from Day 21 to Day 39) Clarified in footnote#2 that PK, immunogenicity and Biomarker samples will not be collected at Week 10.	Optimization of instructions.
3.1 Substudy 2 Background and Rationale	Updated background, added MRCLS section.	
4. Objectives and Endpoints	Reformatted Secondary Objectves and Enpoints into "Secondary – Efficacy", "Secondary – Safety" and "Secondary – Pharmacokinetics". CCI [redacted]	To clarify subcategories of secondary objectives. To allow tools to assess MRCLS participants Optimized wording.
5.1 Overall Design	Clarified that Drug product supply type ('clinical' vs 'commercial') will be recorded in the CRF as part of the route of synthesis.	To allow for subgroup analyses between clinical and commercial supply.

Section # and Name	Description of Change	Brief Rationale
5.1 Overall Design	Provides more detailed Participant Journey 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. Includes provision for allowing target expression screening, leukapheresis and manufacture to be conducted under separate GSK-sponsored protocol or substudy.	To clarify steps and align with the schematics Clarifies that preference for target expression is sequential (HLA-typing then antigen expression) but that parallel testing is allowed. Will facilitate pre-screening, and considerations for re-allocation of participants onto other suited protocols when available.
5.1 Overall Design 6.1 Inclusion Criteria 6.2 Exclusion Criteria	Allows for on-study fresh biopsies to be used for NY-ESO-1 antigen expression screening. If a fresh biopsy is obtained at screening and participant did not receive any supportive anticancer therapy, the same sample can be used for baseline. Optimization of Treatment Fitness and Eligibility criteria prior to Lymphodepletion	Allows for participants who have exhausted any representative tumor specimen to undergo biopsy collection on-study. 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.
5.2 Number of participants	Clarified the need to update the accrual projections for Substudy 2 to approximately 70 participants to account for 15 participants expected to be treated with the clinical drug product supply without any change to sample size for the primary analysis of approximately 55 participants planned to receive commercial drug product supply.	Amended.

6.1 Inclusion criteria	Amended inclusion #2 to include requirement to consult with Medical Monitor if participant is weighing <40kg and is scheduled to receive commercial drug supply.	Addition to ensure safety oversight in treatment of participants weighing <40kg.
	Amended Inclusion#3 to include translocation-specific requirements for MRCLS	Addition
	Amended Inclusion criteria #4 to allow for MRCLS participants with advanced (metastatic or unresectable) disease.	Confirming that participants of either indication with advanced diagnosis may be screened on Substudy 2.
	Amended Inclusion #5 to clarify that "Participants who received anthracycline-based therapy in the neoadjuvant/adjuvant setting" must have progressed within 12 months of completing the regimen to be eligible	Clarification.
	Amended Inclusion #7 to allow for on-study fresh biopsy specimen for screening, and inclusion of reference to guidance on acceptable specimen in Section 5.1	Allows for fresh biopsies on study.
	Added Inclusion #8 to ensure life expectancy at leukapheresis is ≥24 weeks	New addition to ensure participant survival from screening to T-cell infusion.
	Amended Inclusions #9 and #10 (formerly #8 and #9) to allow for HLA-typing and NY-ESO-1 antigen expression test to be conducted under separate GSK-sponsored protocol or substudy.	Will allow for easier pre-screening or transfer of participants between GSK-sponsored protocols.
	Amended Inclusion #11 (formerly #10) to exclude any evidence of clinically significant pericardial effusion.	
	Amended Table 5 of Definitions of Adequate Organ Function: - to specify ANC must be measured without G-CSF support) - to remove requirement for CD3 count - to clarify Lymphocyte count is absolute (ALC) - to clarify steps to assess creatinine clearance for participants between 18 and 65 - to add a nutritional status criterion with Albumin (≥3.5 g/dL)	Added safety precautions. Added clarity and safety precautions.
	Amended Inclusion #21 (formerly #20) to specify that fresh biopsy obtained at screening may be used at baseline if	

Section # and Name	Description of Change	Brief Rationale
	participant did not receive any supportive anti-cancer therapy in between.	Added provision to only collect one fresh biopsy between screening and baseline visit if no supportive anti-cancer therapy was given in between.
7.1.2 Supportive therapy	Section amended for clarification	Added clarification.
7.1.3 Lymphodepleting Chemotherapy	Clarified situations where Medical Monitor must e 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	Added safety oversight and precautions. Added clarification.
9.2.2 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire	Title amended to Item Library 31 (Disease Symptoms)	Title amended per EORTC recommendation.
9.2.7 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire	Title amended to Item Library 30 (Sensory Symptoms)	Title amended per EORTC recommendation.
10.1 Statistical hypotheses	Changed conservative benchmark of 18% to the upper range of the historical ORR of 13%. Added that "the primary analysis will be based on the combined data from both SS and MRCLS. Additional subgroup analyses by indication may be prepared as appropriate."	Optimization.
10.2 Sample size justification	Updated justification using the new benchmark of 13%. Added wording that "Though a smaller sample size could be utilized for the efficacy assessment with adequate power >90%, the larger sample size has been implemented to allow for a more robust safety database."	Optimization.

Section # and Name	Description of Change	Brief Rationale
10.3 Populations for Analyses	Amended definitions as below: - 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" - Safety population was amended to "All participants who received any dose of GSK3377794" - Modified ITT (mITT) population was amended to "All participants who received at least the minimum target dose of GSK3377794" with the minimum target dose being 1x10^9 transduced T cells - mITTc was amended to "All participants who received at least the minimum target dose of GSK3377794 from commercial drug product supply" - the Primary Efficacy Analysis Population (PEAP) was amended to "The first 45 participants who received at least the minimum target dose of GSK3377794 from commercial drug product supply".	Optimization of population definitions.
10.5.5 Interim Analyses	Added wording to specify that "The interim analysis will use efficacy data based on Investigators' assessments instead of the independent central review assessments".	Clarification.

14.4 Amendment 5 (19-MAY-2021)

Overall Rationale for Amendment 5:

The primary rationale for protocol Amendment 5 is to:

1. Inclusion of updated safety language:
    a. for increased monitoring of coagulation and cardiotoxicity biomarkers
    b. for management of CRS and ICANS
    c. for lymphodepleting regimen dose adjustements and assessment of renal function
2. Update on Disease-specific translocation requirements
3. Clarification of End of Interventional Phasephase, End of Follow-up phase and End of substudySubstudy definitions

Section # and Name	Description of Change	Brief Rationale
Core protocol		
9.1.1 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.
9.3.5 Cardiac Assessments	Addition of serum troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests.	Addition of cardiac biomarker tests as part of required baseline visit assessments.
9.3.9.1. Testing for RCL in Clinical Studies And 9.3.10. Testing for Persistence of Transduced T cells and Insertional Oncogenesis	Clarified language to align with Long-term Follow-up Study 208750, including: - discontinuation of persistence/RCL 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 based on FDA guidance.
9.4.5. Pregnancy	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.
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	Addition of Fibrinogen as part of the Coagulation test requirements Addition of Ferritin, serum troponin, NT-proBNP / BNP as part of the Other Tests.	Additions of coagulation and cardiac biomarker tests.

Section # and Name	Description of Change	Brief Rationale
12.3.4. Recording and Follow-Up of AE and SAE	Clarified grading specifications for AEs and SAEs of CRS and ICANS.	Assessment of intensity of AEs and SAEs
12.7.1. T cell Infusion Symptom Management	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	Clarification on restarting Infusion after temporary Infusion related reaction
12.7.2.2 Herpes Simplex and Varicella Zoste and Epstein Barr virusr 12.7.2.4 Hepatitis B prophylaxis 12.7.2.6 Other Anti-Microbial 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. Clarified that prolonged leukopenia may alert for latent viral infections If a patient presents with severe or gross hematuria consider checking for BK viruria and viremia.	Optimizatino of Infection prophylaxis language.
12.7.5. Management of Cytokine Release Syndrome	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 respondsing to tocilizumab.	Additions of monitoring requirments for CRS accoding to SITC 2020 guideline on immune effector cell-related adverse events.
12.7.8. Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Addition of monitoring requirement for suspected ICANS, with chemistry, hematology, ferritin, coagulation and C-reactive protein. Clarification of ICANS management table. Addition that tocilizumab may worsen ICANS in some situations.	Additions of monitoring requirements for ICANS accoding to SITC 2020 guideline on immune effector cell-related adverse events.

Section # and Name	Description of Change	Brief Rationale
Substudy 1		
2. Schedule of Assessment Table 1 & Table 2	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.	Clarification of window for consent.
	Footnote #13 (Table 1) Window for CT/MRI or FDG PET/CT scan performed as standard of care prior to study consent will be acceptable as long as assessment is done within 90 days before leukapheresis.	Clarification of window for scans for eligibility
	Footnote #14 (Table 1) has been added to state that MRI of the spine will be performed when clinically indicated.	Addition of MRI of spine if clinically indicated
	Added requirement forTroponin and NT-proBNP / BNP test prior to Lymphodepletion (Table 2)	Addition of cardiac marker and coagulation tests.
	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 reuirement for monitoring of troponin and NT-proBNP / BNP labs for CRS Grade ≥2 as clinically indicated.	Clarification of schedule of assessment for suspected CRS or ICANS.
3.2.1 Risk Assessment	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 GSK3377794 infusion.	Safety update.

Section # and Name	Description of Change	Brief Rationale
5.3 End of Study definition	Clarified the end of interventional phase, and end of study for individual participants and the study as a whole in order to ensure continuous follow-up of participants until transition to long-term follow-up protocol 208750.	Clarification.
6.1 Inclusion criteria	Amended Table 4 of Definitions of Adequate Organ Function: - to add footnote c recommending consultation with hematologist prior to lymphodepletion in participants who have had a serious/significant bleeding/thrombosis history. - to add footnote d referring to Section 7.5.2 for guideline on use of anticoagulant medications	Added safety oversight, precautions and management guidelines.
6.1 Inclusion criterion #20 (added)	Hematologist consultation prior to lymphodepletion for participants with serious/significant bleeding/thrombosis history.	Added hematologist consultation when indicated
6.1 Inclusion #3	Clarification on translocation requirement for inclusion of SS and MRCLS 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.	Clarification of methods of detection of translocations.
7.1.1 Leukapheresis	Clarification that a CD3 count of ≥200/μL is recommended to ensure adequate collection of T cells. In situations where CD3 count is lower than 200, test is to be repeated and Sponsor is to be alerted, as more than one leukapheresis procedure may be needed.	Clarification on CD3 count
7.5.2. Permitted Concommitant Medication and Treatment	Added recommendations for management of participants on therapeutic anticoagulants:	Optimization of safety oversight and precautions.

Section # and Name	Description of Change	Brief Rationale
Substudy 2		
2. Schedule of Assessment Tables 1 & 2	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. Footnote #13 (Table 1) Window for CT/MRI or FDG PET/CT scan performed as standard of care prior to study consent will be acceptable as long as assessment is done within 90 days before leukapheresis. Footnote #14 (Table 1) has been added to state that MRI of the spine will be performed when clinically indicated. Added requirement forTroponin 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 sympotms are improving or an alternative diagnosis is confirmed. Included reuirement for monitoring of troponin and NT-proBNP / BNP labs for CRS Grade ≥2 as clinically indicated.	Clarification of window for consent. Clarification of window for scans for eligibility Addition of MRI of spine if clinically indicated Addition of cardiac marker and coagulation tests. Clarification of schedule of assessment for suspected CRS or ICANS.
3.2.1 Risk Assessment	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 GSK3377794 infusion.	Safety update.

Section # and Name	Description of Change	Brief Rationale
5.3 End of Study definition	Clarified the end of interventional phase, end of follow-up phase, and end of study for individual participants and the study as a whole in order to ensure continuous follow-up of participants until transition to the long-term follow-up protocol 208750.	Clarification.
6.1 Inclusion criteria	Amended Table 4 of Definitions of Adequate Organ Function: - to add footnote c recommending consultation with hematologist prior to lymphodepletion in participants who have had a serious/significant bleeding/thrombosis history. - to add footnote d referring to Section 7.5.2 for guideline on use of anticoagulant medications	Added safety oversight, precautions and management guidelines.
6.1 Inclusion criterion #21 (added)	Hematologist consultation prior to lymphodepletion for participants with serious/significant bleeding/thrombosis history.	Added hematologist consultation when indicated
6.1 Inclusion #3	Clarification on translocation requirement for inclusion of SS and MRCLS 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.	Clarification of methods of detection of translocations.
7.1.1 Leukapheresis	Clarification that a CD3 count of ≥200/μL is recommended to ensure adequate collection of T cells. In situations where CD3 count is lower than 200, test is to be repeated and Sponsor is to be alerted as more than one leukapheresis procedure may be needed.	Clarification on CD3 count
7.5.2. Permitted Concommitant Medication and Treatment	Added recommendations for management of participants on therapeutic anticoagulants:	Added safety oversight and precautions.

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