Protocol Amendment 4

Study ID: 209012 Substudy 1

Sub-study Official Title: Assessment of Safety and Recommended Phase 2 Dose of Autologous T cells Engineered with an Affinity-enhanced TCR Targeting NYESO1 and LAGE1a, and co-expressing the CD8α (GSK3901961) in Participants with NYESO1 and/or LAGE1a Positive Previously Treated Advanced (Metastatic or Unresectable) Synovial Sarcoma / Myxoid/Round Cell Liposarcoma; or NYESO1 and/or LAGE1a Positive Previously Treated Metastatic Non-Small Cell Lung Cancer

NCT ID for sub-study: NCT06048705

Date of Document: 27-MAY-2022

TITLE PAGE

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

Protocol Number: 209012/Amendment 04 Substudy 1

Compound Number: GSK3901961

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

Sponsor Name and Legal Registered Address:
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5 Crescent Drive
Philadelphia, PA 19112
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Regulatory Agency Identifying Number(s):

IND Number: 19751

EudraCT Number: 2019-004446-14

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

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Approval Date: 27 May 2022

SUBSTUDY 1: GSK3901961 IN PREVIOUSLY TREATED ADVANCED (METASTATIC OR UNRESECTABLE) SYNOVIAL SARCOMA / MYXOID/ROUND CELL LIPOSARCOMA, AND PREVIOUSLY TREATED METASTATIC NON-SMALL CELL LUNG CANCER

Substudy title: Assessment of Safety and Recommended Phase 2 Dose of Autologous T cells Engineered with an Affinity-enhanced TCR Targeting NYESO1 and LAGE1a, and co-expressing the CD8α (GSK3901961) in Participants with NYESO1 and/or LAGE1a Positive Previously Treated Advanced (Metastatic or Unresectable) Synovial Sarcoma / Myxoid/Round Cell Liposarcoma; or NYESO1 and/or LAGE1a Positive Previously Treated Metastatic Non-Small Cell Lung Cancer

This document contains substudy 1 specific details. Refer to the body of the Core Section of the Master Protocol Amendment 04 for all other information.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY SUBSTUDY 1		
Document	**Date**	**DNG Number**
Amendment 04	27 May 2022	TMF-14682591
Amendment 03	20 December 2021	TMF-14357929
Amendment 02	04 November 2021	TMF-14137790
Amendment 01	21 May 2021	TMF-13779299
Original Protocol	02 December 2019	2019N419717_00

Amendment 04 - 27 May 2022

The primary reasons for Amendment 04 are as follows:

- Changes to correct text inadvertently modified during the publication of Amendment 02. Edits in Amendment 04 reflect intended language
- Updated eligibility criteria on prior therapies across indications to incorporate standard of care practice and investigator's discretion
- Minor changes to Substudies 1, 2, and 3 to ensure alignment of design and procedures across the 3 substudies

Section # and Name	Description of Change	Brief Rationale
Substudy 1		
Throughout the protocol	Made administrative changes and corrected clerical errors. Clarified language on lower dose range to "0.1-0.8 x10^9" instead of "1-8x10^8"	For clarity and consistency For clarity and consistency
Section 2 – Schedule of Activities – Table 1	Added footnote (#14): If leukapheresis is rescheduled, existing brain MRI results will be accepted if obtained within 2 months prior to the rescheduled procedure and the participant has no new neurological symptoms	For flexibilty
Section 2 – Schedule of Activities – Table 2 and Table 4	Removed requirement for creatinine clearance assessments originally scheduled at Months 18 and 30 Transgene Copies (persistence for safety) and CCI [redacted] to be collected every 6 months from Month 12 and onwards, while the patient is in follow-up	Serum creatinine test has been maintained at these timepoints as part of chemistry panel and can still provide an estimation of creatinine clearance In alignment with GSK Long-Term Follow-Up study 208750

Section # and Name	Description of Change	Brief Rationale
	Removed footnote #3, which stipulated the days on which lymphodepletion would occur for all tumors	Footnote no longer needed since lymphodepletion schedule is aligned across indications
	Added footnote #6 to indicate that Day -7 visit is not required for participants who initiate lymphodepletion on Day -6. Complete physical exam must occur on Day -6 for these participants.	To clarify visit requirements for participants who initiate lymphodepletion on Day -6
	Modified existing language (footnote #14) on CT/MRI for clarity	For clarity
	Modified existing language (footnote #17) on Brain MRI at baseline to clarify that it should be obtained among participants with no history of CNS metastasis if more than 3 months have elapsed between the last brain MRI and the start of lymphodepletion or if they show neurological symptoms consistent with CNS metastasis. Brain MRI at baseline should be obtained for all participants with a history of brain metastasis.	To clarify assessment window and for safety purposes
Section 2 – Schedule of Activities –Table 4	Footnotes concerning pulse oximetry were revised to align with footnotes in Table 2	To align tables for clarity
Section 2 – Schedule of Activities – Table 3 and Table 5	Footnote #8 was revised to clarify that 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).	For clarity
	Removed dnTGF-βRII Expression Analyses	These analyses are not applicable to Substudy 1
Section 2 – Schedule of Activities – Table 5	Removed mention of circulating cell-free RNA	Test no longer being conducted, as of PA-2
Section 5.1.1.2	Modified footnote for "U" in Table 8 to include action to "de-escalate to the lower dose if applicable"	For clarity
	Modified language on analyses for the dose de-escalation or RP2D confirmation decision	In alignment with DSC plan
Section 5.1.2 – Dose Expansion Phase	Removed language related to primary analysis	Listed in Section 10.5.2

Section # and Name	Description of Change	Brief Rationale
Section 5.1.4 – Tumor Biopsies	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) Removed details discussed within the Laboratory Manual	Archived biopsy (even if not from screening period) may be accepted at the discretion of the Medical Monitor To eliminate redundancy
Section 5.3.1 – End of Substudy for Individual Participants	Removed inaccurate AE follow-up requirements and referred to the relevant section of the Core protocol	For clarity and to eliminate repetitive language
Section 6.1.1– Inclusion Criteria – Target Expression Screening	Criterion #2 was revised to add that participants must weigh ≥40 kg to proceed with target expression screening	For participant safety and in line with current product manufacturing capabilities
Section 6.1.2 - Inclusion Criteria - Leukapheresis Eligibility Screening	Modified language on criterion #13 on prior lines of therapy for SS/MRCLS participants to align with Substudy #3 Modified language on criterion #14 on prior lines of therapy for NSCLC participants: • NSCLC participants not harboring actionable genetic aberrations must have received a PD-1/PD-L1 checkpoint blockade therapy and a platinum containing chemotherapy, or participant is intolerant to it • NSCLC participants with actionable genetic aberrations must have received standard of care therapy • To allow investigator to decide if therapies after the first line are not in the participant's best interest • Added definition for "intolerance" criterion #14 for NSCLC, in alignment with criterion #13 for SS/MRCLS	To align across substudies In alignment with protocol amendment 01. Language was inadvertently modified in protocol amendment 02. To align with standard practice At investigator's discretion, in alignment with Medical Monitor In alignment with criterion #13 for SS/MRCLS
Section 6.1.2 - Inclusion Criteria - Leukapheresis Eligibility Screening	Aligned language on measurable disease between eligibility criterion #10 and eligibility criterion #22 Aligned language on LAGE-1a testing between eligibility criterion #9 and corresponding note	For consistency
Section 6.1.3 - Inclusion Criteria - Treatment Eligibility Screening	Added language on eligibility criterion #23 (baseline biopsy) for single measurable lesions	For clarity

Section # and Name	Description of Change	Brief Rationale
Section 6.2.2 - Exclusion Criteria – Leukapheresis Eligibility Screening	Criterion #6 was revised to clarify that the exceptions for central nervous system metastases only apply to participants with NSCLC. No central nervous system metastases are permitted for participants with SS or MRCLS. Additionally, sub-bullet "k" was modified in alignment with updated Brain MRI requirements Criterion #14 was corrected to accurately reflect that active Epstein Barr virus infection or cytomegalovirus infection are exclusion criteria	For clarity and in alignment with protocol amendment 01 For clarity
Section 6.2.3 - Exclusion Criteria – Treatment Eligibility Screening Table 10	Radiotherapy washout periods corrected to reflect washout periods for NSCLC patients, per exclusion criterion #6	In alignment with exclusion criterion #6
Section 10.2.1 – Sample Size for Cohort 1 and Section 10.2.2 – Sample Size for Cohort 2	Additional information (i.e., use of uninformative Beta prior) was added to sample size determination for each cohort	For clarity
Section 10.5 – Statistical Analyses for Cohort 1 and 2	Correction to number of subjects required for Cohort 2 (SS/MRCLS) early interim analysis, to align with corresponding futility rule in Section 10.2.2	In alignment with Section 10.2.2
CCI [redacted]		

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1 SYNOPSIS

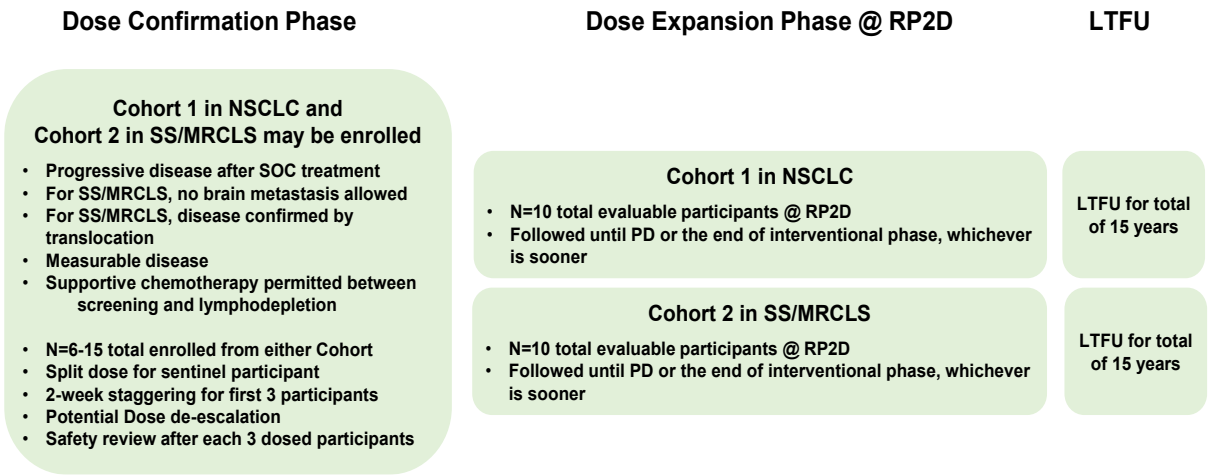
GSK3901961 belongs to the second generation of NYESO1 TCR engineered T cells that incorporate additional sequences on the lentiviral vector construct to encode genes for molecules that would enhance T-cell function within the tumor micro-environment (TME).

GSK3901961 consists of NYESO1^{c259} TCR engineered autologous T cells that are modified by multi-component engineering (MCE) transduction to co-express the α-chain of the CD8 co-receptor in order to:

- Enhance proliferation and persistence of the genetically engineered T cells;
- Increase helper functions including the Type 1 T helper (Th1) anti-tumor response and recruitment of other immune cell types;
- Enhance activity of tumor-specific effector cells through stimulation by CD4+ T cells.

This is a first time in human (FTIH) multi-cohort, non-randomized, open-label substudy to investigate GSK3901961 in previously treated participants with advanced (metastatic or unresectable) synovial sarcoma (SS) / myxoid/round cell liposarcoma (MRCLS) or previously treated metastatic NSCLC). This substudy will consist of two phases: Dose Confirmation Phase and Dose Expansion Phase as follows:

Substudy 1 Design



NOTE: Participants included in different substudies may have the same eligibility criteria.
Sponsor will inform Investigators of the participant assignments between substudies and indicate if the participant is a sentinel participant and the number of remaining slots.

LTFU = long-term follow-up; MRCLS = myxoid/round cell liposarcoma; NSCLC = non small cell lung cancer; PD = progressive disease; RP2D = recommended phase 2 dose; SS = synovial sarcoma.

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/CCI [redacted] 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

Substudy 1: 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[1]	X			1. Written informed consent must be obtained prior to performing any study assessments or procedures, except as stated in footnote 11. 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 and/or LAGE-1a 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 Leukapheresis Eligibility Screening and at Treatment Fitness & Eligibility/Baseline visits; however, any changes in medical history must be recorded in source documents throughout the conduct of the study. 6. Tobacco use needs to be assessed for all participants. 7. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported. 8. Can be performed at any time within 7 days prior to the day of leukapheresis. 9. CD3 count prior to leukapheresis should be preferably performed within 24 hours prior to leukapheresis procedure. 10. Includes temperature, blood pressure, pulse rate, respiratory rate, and pulse oximetry.
Informed Consent for Leukapheresis and Treatment[1]		X		
Inclusion/Exclusion for Screening	X			
Inclusion/Exclusion for Leukapheresis		X		
Demographics	X			
Central Laboratory HLA -A*02:01, A*02:05, or A*02:06 genotyping[3]	X			
Tumor expression of NY-ESO- 1 and/or LAGE-1a[3]	X			
Liquid biopsy (blood)[4]	X			
Medical History[5] and Tobacco use[6]		X		
Prior/Concomitant Medications[7]		X	X	
Height and Weight		X		
Physical Exam (complete)		X	X[8]	
ECOG		X		
Vital Signs[10]		X	X[8]	
12-lead ECG (in triplicate)		XXX	XXX[8]	
ECHO/MUGA		X[11]		
CT / MRI		X[12]		

Substudy 1: Screening and Leukapheresis				
	Screening Phase[1]		Leukapheresis	Notes
	Target Expression Screening[2]	Leukapheresis Eligibility Screening, within 28 days prior to leukapheresis[3]		
Brain MRI[13]		X[11, 14]		11. ECHO/MUGA, brain MRI and laboratory assessments performed as standard of care prior to study consent will be acceptable as long as the assessment is done within 28 days before leukapheresis. 12. CT/MRI scan confirming disease progression can be performed at any time following participant's last round of prior treatment. Any FDG PET/CT performed as part of clinical routine at the same time, will also be collected. 13. In addition to the Brain MRI, MRI of the spine will be performed when clinically indicated. 14. If leukapheresis is rescheduled, existing brain MRI results will be accepted if obtained within 2 months prior to the rescheduled procedure and the participant has no new neurological symptoms. 15. PFTs will include FEV1, FVC, TLC, and DLCO will be measured to determine eligibility. PFTs may be assessed at other time points if medically necessary. 16. WOCBP must have a highly sensitive negative urine or serum pregnancy test at Screening for leukapheresis and within 24 h prior to leukapheresis. 17. Includes HIV, HBV, HCV, HTLV, EBV, CMV, and syphilis (spirochete bacterium). 18. See Section 6.1 Table 9 of this substudy for specifics on renal assessment. 19. 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.
Hematology		X[11]	X[8]	
Clinical Chemistry		X[11]	X[8]	
Coagulation Tests		X[11]	X[8]	
Lymphocyte Subset (CD3/CD4/CD8)		X	X[8,9]	
Pulmonary function test (PFTs)[15]		X		
FSH, if needed to determine CBP		X		
Pregnancy Test[16]		X[16]	X[16]	
Urinalysis		X[11]	X[8]	
Infectious disease markers[176]		X[11]		
Creatinine clearance by eGFR or 24h urine[18]		X		
Adverse Events and Serious Adverse Events	X[19]	X[19]	X	
Leukapheresis			X	

AE = Adverse event; CBP=child-bearing potential; CMV = Cytomegalovirus; CT = computerized tomography; DLCO=diffusing capacity of the lung for carbon monoxide; EBV = Epstein Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FDG = Fluorodeoxyglucose; FEV1= Forced expiratory volume in 1 second; FSH=follicle-stimulating hormone; FVC= Forced vital capacity; 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; PD=progressive disease; PFT = pulmonary function test; SAE = Serious adverse event; TLC=total lung capacity; WOCBP = women of childbearing potential.

Table 2 Substudy 1 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment, and Follow-up)

Substudy 1: Interventional Phase (Lymphodepletion, Treatment and Follow-up)																				
	Treatment Fitness & Eligibility / Baseline	**Lymphodepletion**				**T-cell Infusion[1]**	**Post T-cell Infusion**												**3-6**	**9, then Q3M until confirmed PD or phase end,[2] whichever is sooner**
Month (1 month = 4 weeks)	**-1**					**1**								**2**						
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]	**-6**[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**
Admission to hospital						X														
Discharge from hospital									X[3]											
Treatment Fitness and Inclusion/Exclusion for Treatment Eligibility	X																			
Request GSK3901961 shipment	X[4]																			
Med. History & Tobacco use[5]	X																			
Physical Exam (complete)[6]	X	X[6]				X	X	X	X	X	X		X			X	X		X	X
Physical Exam (dedicated)												X		X	X					
Prior/Con Meds[7]	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
ECOG	X					X					X		X		X		X		X	X
Vital Signs[8] and weight	X	X[6]	X	X	X	X[9]	X	X	X	X	X	X	X	X	X	X	X		X	X
ECHO/MUGA[20]	X																			
Telemetry[10]						X[10]														

Substudy 1: Interventional Phase (Lymphodepletion, Treatment and Follow-up)																				
	Treatment Fitness & Eligibility / Baseline	**Lymphodepletion**				**T-cell Infusion[1]**	**Post T-cell Infusion**											**3-6**	**9, then Q3M until confirmed PD or phase end,[2] whichever is sooner**
Month (1 month = 4 weeks)	**-1**					**1**								**2**					
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]	**-6**[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**
Pulse oximetry[11]						X[11]	X	X	X	X	X	X[12]	X	X[12]	X	X	X	X	
12-lead ECG[13]	XXX					X			X		X								
CT/MRI[14]	X														X[15]			X[16]	X
Brain MRI[17]	X[17]																		
ICE[18]						X[19]	X	X	X	X	X								
Chest X-Ray	X																		
Hematology[20]	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[20]	X	X[6]	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			

Substudy 1: Interventional Phase (Lymphodepletion, Treatment and Follow-up)																				
	Treatment Fitness & Eligibility / Baseline	**Lymphodepletion**				**T-cell Infusion[1]**	**Post T-cell Infusion**													
Month (1 month = 4 weeks)	**-1**					**1**								**2**				**3-6**	**9, then Q3M until confirmed PD or phase end,[2] whichever is sooner**	
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]	**-6**[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**	
Thyroid function tests[29]	X																			
CRP[20]	X					X			X		X	X	X	X	X	X	X	X	X	
Adverse Events and Serious Adverse Events[21]	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Transgene Copies (Persistence for Safety)[31] and CCI [redacted]	X																	Weeks 12 and 24	Month 12 and Q6M[32]	
Genetic sample	X																			
Lymphodepletion																				
Fludarabine		X[6,33]	X	X	X															
Cyclophosphamide			X	X	X															
IP Administration																				
GSK3901961						X[34]														

1. On Day 1, all samples will be collected and assessments performed prior to T-cell infusion (within 24 h), unless otherwise specified.
2. See Section 5.3.1 of this substudy for the definition of the end of Interventional phase.
3. After all of the procedures are complete and participant is deemed ready for discharge by the Investigator.
4. As GSK3901961 needs to be on site prior to lymphodepletion, request GSK3901961 no later than 4 working days prior to the day of lymphodepletion. The mechanism of request will be provided in Drug Product and Infusion Manual.

5. Tobacco use needs to be assessed in all participants. Medical history and tobacco use will be recorded in the eCRF at Screening and Baseline visits; however, any changes in medical history and tobacco use must be recorded in source documents throughout the conduct of the study.
6. For participants who initiate lymphodepletion on Day -6, the Day -7 visit is not required. A complete physical exam for these participants must occur on Day -6.
7. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.
8. Vital signs include temperature, blood pressure, pulse rate, and respiratory rate.
9. Vital signs on day of T-cell infusion should be taken pre-infusion, and at 5, 15, and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
10. Inpatient telemetry must be done for participants with Baseline tumor masses in close proximity to the heart for a minimum of three and up to seven days post T-cell infusion.
11. On T-cell infusion day, pulse oximetry should be taken pre-infusion, and at 5, 15, and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
12. Pulse oximetry at these visits will be performed if medically indicated.
13. ECG can also be performed at other time points if medically indicated. Triplicate ECG will be collected at Baseline and single ECGs at other timepoints. Participants with clinically significant cardiovascular risk factors (as per Core Section 9.1.6) will undergo evaluation by a cardiologist prior to lymphodepletion
14. See Core Section 9.3.1 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 in the Core Protocol), 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. Any FDG PET/CT or other scans used for tumor assessments performed as per clinical routine will be collected centrally.
15. CT/MRI at this visit has a window of ± 7 days.
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 in all participants with a history of CNS metastasis. It should be performed at Baseline in participants with no history of CNS metastasis if more than 3 months have elapsed between the last brain MRI and the start of lymphodepletion or if they show neurological symptoms consistent with CNS metastasis. Brain MRI 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. Participants with known brain metastases should be monitored at least twice per day for the first 5 days following GSK3901961 infusion. If a participant is found to have ICANS, the ICE neurological assessment tool should be used at least twice per day until ICANS is resolved or stable (See Section 12.7.8 in the Core Protocol). It can also be used at later visits if indicated.
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 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 5). In addition, troponin, and N-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests should be monitored for participants with CRS Grade ≥2 as clinically indicated. 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 Core Section 12.7.5).
21. See Section 6.1 Table 9 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 assessed prior to initiation of lymphodepletion.
24. WOCBP must have a negative urine or serum pregnancy test within 24 h prior to GSK3901961 infusion. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
25. WOCBP will need to have pregnancy tests performed at all visits indicated in the table for the duration of the contraception period.
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 (spirochete 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. Thyroid function tests will also be performed at other time points, if clinically indicated.
30. In all cases of SAE that occur after T-cell infusion, a transgene copy (persistence) sample must be obtained if feasible.
31. If possible, this sample also needs to be obtained in case of any SAE that occurs after T-cell infusion.
32. If no gene modified cells are detected for 2 consecutive assessments post-infusion and the participant is ≥2 years post T-cell infusion, samples for CCI [redacted], and persistence of gene modified cells will be discontinued (Section 9.1.12 of the Core Protocol).
33. On Day -7, fludarabine will not be administered to participants ≥60 years old.
34. For participants who receive GSK3901961 as split doses of ~30% and ~70%, please see Table 4 and Table 5.

AE = Adverse event; aPTT =Activated PTT; BNP = B-type natriuretic peptide; CMV = Cytomegalovirus; Con Meds = concomitant medications; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computerized tomography; EBV = Epstein Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; GBS = Guillain Barre syndrome; 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; INR = International Normalized Ratio; Med history=medical history; MRI = magnetic resonance imaging; MUGA = multigated acquisition;; NT-proBNP = N-terminal pro-BNP; PCR = polymerase chain reaction; PD = progressive disease; PK = Pharmacokinetics; PTT = partial thromboplastin time; Q3M = every 3 months; Q6M = every 6 months; CCI [redacted]; SAE = Serious adverse event; TSH = Thyroid stimulating hormone; CCI [redacted]; WOCBP = Women of childbearing potential

Table 3 Substudy 1 Schedule of Activities – PK, Immunogenicity, and CCI [redacted] - Interventional Phase (Treatment and Follow-up)

Substudy 1: PK, Immunogenicity, and CCI [redacted] - Interventional Phase (Treatment and Follow-up)														
	Sample Type	**Baseline**	**T-cell infusion**					**Post T-cell infusion**						
Month (1 month = 4 weeks)		**-1**	**1**								**2**		**3-6**	**9, then Q3M until confirmed PD or phase end, whichever is sooner[1,2]**
Week		**-3 to -2**	**1**					**2**	**3**	**4**	**6**	**8**	**12, 18, 24 or until confirmed PD, whichever is sooner[1]**	
Day		**-17 to -8[3]**	**1[4]**	**2**	**3**	**4**	**6**	**8**	**15**	**22**	**36**	**50**	**78, 120, 162**	
Visit Window		**N/A**						**±1 day**			**±3 days**		**±7 days**	**±1 month**
Cell phenotype and Functional Assays	PBMC	X				X		X	X	X	X	X	X	X
Transgene Copies (Pharmacokinetics)	PBMC	X		X		X		X	X	X	X	X	X	X
Cytokine Analyses[5]	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	X
CCI [redacted]	Serum		X						X		X	X	Week 12, Week 24	X
Liquid biopsy (blood)[6]	Whole blood	X						X		X	X		X	X
Tumor Biopsy[7]	Biopsy	X[8]								X[9]			X[10]	

1. All assessments need to be performed at all visits specified in the Table, up to and including the visit establishing confirmed PD or study withdrawal or discontinuation. There are no assessments that need to be performed at Weeks 5, 7, and 10; therefore, Weeks 5, 7, and 10 are not present in this Table.
2. See Section 5.3.1 of this substudy for the definition of the end of Interventional phase.
3. Baseline assessments will be performed until Day -8.
4. All assessments to be performed prior to T-cell infusions.
5. If CRS is suspected, cytokine samples should be collected every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.
   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).
6. Blood sample from which circulating cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes may be extracted, should match tumor biopsy visits and imaging (Body CT/MRI) visits as well as be taken on Day 8 and Day 22.

7. 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 if clinically indicated.
8. 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). For participants who already provided a fresh screening biopsy and did not receive any subsequent bridging or standard of care anti-cancer therapy, this may be used as the Baseline sample if obtained preferably within 90 days prior to initiating lymphodepleting chemotherapy.
9. Week 4 biopsy must be taken preferably between Days 21-23 (Week 4) if medically feasible, but window for collection is extended until Week 6 visit (Day 39).
10. Must be taken once at confirmed disease progression if medically feasible.

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

Table 4 Substudy 1 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment and Follow-up) for Split Dosing

Substudy 1: Interventional Phase (Lymphodepletion, Treatment and Follow-up) for Split Dosing																											
	TFE / BL	**Lymphodepletion**				**T-cell infusion[1]**														**Post T-cell Infusion**						
Month (1 month = 4 weeks)	**-1**					**1**														**2**				**3**	**3-6**	**9, then Q3M until confirmed PD or phase end,[2] whichever is sooner**
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**	**9**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**	
Day	**-17 to -8**	**-7**[6]	**-6**[6]	**-5**	**-4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**13**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64, 78, 120, 162**	
Visit Window	**N/A**																**±1 days**			**±3 days**					**±7 days**	**±1 month**
Admission to hospital						X																				
Discharge from hospital																X[3]										
Treatment Fitness and Inclusion/Exclusion for Treatment Eligibility	X																									
Request GSK3901961 shipment	X[4]																									
Med. History & Tobacco use[5]	X																									
Physical Exam (complete)[6]	X	X[6]				X	X	X	X	X	X	X	X	X	X	X	X		X			X	X	X	X	X
Physical Exam (dedicated)																		X		X	X					
Prior/Con Meds[7]	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X					X							X						X		X		X		X	X
Vital Signs[8] and weight	X	X[6]	X	X	X	X[9]	X	X	X	X	X	X	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECHO/MUGA	X																									
Telemetry[10]						X[10]							X[10]													
Pulse oximetry						X[11]	X	X	X	X	X	X	X[11]	X	X	X	X	X[12]	X	X[12]		X	X	X	X	
12-lead ECG[13]	XXX					X			X				X			X		X								
CT/MRI[14]	X																				X[15]				X[16]	X
Brain MRI[17]	X[17]																									

Substudy 1: Interventional Phase (Lymphodepletion, Treatment and Follow-up) for Split Dosing																											
	TFE / BL	**Lymphodepletion**				**T-cell infusion[1]**														**Post T-cell Infusion**						
Month (1 month = 4 weeks)	**-1**					**1**														**2**				**3**	**3-6**	**9, then Q3M until confirmed PD or phase end,[2] whichever is sooner**
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**	**9**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**	
Day	**-17 to -8**	**-7**[6]	**-6**[6]	**-5**	**-4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**13**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64, 78, 120, 162**	
Visit Window	**N/A**																**±1 days**			**±3 days**					**±7 days**	**±1 month**
ICE[18]						X[19]	X	X	X	X	X	X	X[19]	X	X	X	X	X								
Chest X-Ray	X																									
Hematology	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[20]	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Uric acid	X					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	X	X	X	X	X	X								
Ferritin[20]	X																									
Troponin and NT-proBNP /BNP[20, 23]	X																									
Pregnancy	X					X[24]							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		X				
Thyroid function tests[29]	X																									
CRP[20]	X					X			X			X		X		X		X	X	X	X	X	X	X	X	X
AEs and SAEs[30]	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transgene Copies (Persistence for Safety)[31] and [redacted]	X																								Weeks 12 and 24	Month 12 and Q6M[32]
Genetic sample	X																									

Substudy 1: Interventional Phase (Lymphodepletion, Treatment and Follow-up) for Split Dosing																												
	TFE / BL	**Lymphodepletion**				**T-cell infusion[1]**														**Post T-cell Infusion**							
Month (1 month = 4 weeks)	**-1**					**1**														**2**				**3**	**3-6**	**9, then Q3M until confirmed PD or phase end,[2] whichever is sooner**	
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**	**9**	**10, 12, 18, 24 or until confirmed PD, whichever is sooner**	
Day	**-17 to -8**	**-7**[6]	**-6**[6]	**-5**	**-4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**13**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64, 78, 120, 162**	
Visit Window	**N/A**																**±1 days**			**±3 days**					**±7 days**	**±1 month**	
Lymphodepletion																												
Fludarabine		X[6,33]	X	X	X																							
Cyclophosphamide			X	X	X																							
IP Administration																												
GSK3901961						X							X															

1. On Day 1 and Day 8, all samples will be collected, and assessments performed prior to T-cell infusion (within 24 hours), unless otherwise specified.
2. See Section 5.3.1 of this substudy for the definition of the end of Interventional phase.
3. After all the procedures are complete and participant is deemed ready for discharge by the Investigator.
4. As GSK3901961 needs to be on site prior to lymphodepletion, request GSK3901961 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.
5. Tobacco use needs to be assessed in all participants. Medical history and tobacco use will be recorded in the eCRF at Screening and Baseline visits; however, any changes in medical history and tobacco use must be recorded in source documents throughout the conduct of the study.
6. For participants who initiate lymphodepletion on Day -6, the Day -7 visit is not required. A complete physical exam for these participants must occur on Day -6.
7. Includes all prescription, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.
8. Vital signs include temperature, blood pressure, pulse rate, and respiratory rate.
9. Vital signs on days of T-cell infusion should be taken pre-infusion, and at 5, 15, and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
10. Inpatient telemetry must be done for participants with Baseline tumor masses in close proximity to the heart for a minimum of three and up to seven days post T-cell infusion.
11. On T-cell infusion days, pulse oximetry should be taken pre-infusion, and at 5, 15, and 30 minutes, and 1, 1.5, 2, and 4 hours after the infusion has started.
12. Pulse oximetry at these visits will be performed if medically indicated.
13. ECG can also be performed at other time points if medically indicated. Triplicate ECG will be collected at Baseline and single ECGs at other timepoints. Participants with clinically significant cardiovascular risk factors (as per Core Section 9.1.6) will undergo evaluation by a cardiologist prior to lymphodepletion

14. See Section 9.3.1 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 in the Core Protocol), 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. Any FDG PET/CT or other scans used for tumor assessment performed as per clinical routine will be collected centrally.
15. CT/MRI at this visit has a window of ±7 days.
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 in all participants with a history of CNS metastasis. It should be performed at Baseline in participants with no history of CNS metastasis if more than 3 months have elapsed between the last brain MRI and the start of lymphodepletion or if they show neurological symptoms consistent with CNS metastasis. Brain MRI 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. Participants with known brain metastases should be monitored at least twice per day for the first 5 days following GSK3901961 infusion. If a participant is found to have ICANS, the ICE neurological assessment tool should be used at least twice per day until ICANS is resolved or stable (See Section 12.7.8 in the Core Protocol). It can also be used at later visits if indicated.
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 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 5 footnote 5). In addition, troponin, and N-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests should be monitored for participants with CRS Grade ≥2 as clinically indicated. 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 Core Section 12.7.5).
21. See Section 6.1 Table 9 for specifics on renal assessment.
22. Coagulation tests include INR, PTT or aPTT and fibrinogen. Coagulation tests should be taken at baseline, Days 1 thru 11, 13 and 15.
23. Troponin and NT-proBNP / BNP tests should be assessed prior to initiation of lymphodepletion.
24. WOCBP must have a negative urine or serum pregnancy test within 24 h prior to each GSK3901961 infusion. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
25. WOCBP will need to have pregnancy tests performed at all visits indicated in the table for the duration of the contraception period.
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 (spirochete 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. Thyroid function tests will also be performed at other time points, if clinically indicated.
30. In all cases of SAE that occur after T-cell infusion, a transgene copy (persistence) sample must be obtained if feasible.
31. If possible, this sample also needs to be obtained in case of any SAE that occur after T-cell infusion.
32. If no gene modified cells are detected for 2 consecutive assessments post-infusion and the participant is ≥2 years post T-cell infusion, samples for CCI [redacted] and persistence of gene modified cells will be discontinued (Section 9.1.12 of the Core Protocol).
33. On Day -7 ,fludarabine will not be administered to participants ≥60 years old.

AE = adverse event; aPTT = Activated PTT; BNP = B-type natriuretic peptide; CMV = Cytomegalovirus; Con Meds = concomitant medications; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computerized tomography; EBV = Epstein Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative

Oncology Group; GBS = Guillain Barre syndrome; 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; INR = International Normalized Ratio; Med history=medical history; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NT-proBNP = N-terminal pro-BNP; PCR = Polymerase chain reaction; PD = progressive disease; PK = Pharmacokinetics; PTT = partial thromboplastin time; Q3M = every 3 months; Q6M = every 6 months; CCI ; SAE = serious adverse event; TFE / BL = Treatment Fitness & Eligibility / Baseline; TSH = Thyroid stimulating hormone; CCI ; WOCBP = Women of childbearing potential.

Table 5 Substudy 1 Schedule of Activities – PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) for Split Dosing

Substudy 1: PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) for Split Dosing																				
	Sample Type	**BL**	**T-cell infusion**											**Post T-cell Infusion**						
Month (1 month = 4 weeks)		**1**												**2**				**3-6**	**9, then Q3M until confirmed PD or phase end, whichever is sooner[1,2]**	
Week		**-3 to -2**	**1**						**2**					**3**	**4**	**6**	**8**	**12, 18, 24 or until confirmed PD, whichever is sooner[1]**		
Day		**-17 to -8[3]**	**1[4]**	**2**	**3**	**4**	**6**	**7**	**8[4]**	**9**	**10**	**11**	**13**	**15**	**22**	**36**	**50**	**78, 120, 162**		
Visit Window		**N/A**	**N/A**										**±1 days**			**±3 days**		**±7 days**	**±1 month**	
Cell phenotype and Functional Assays	PBMC	X				X			X			X		X	X	X	X			
Transgene Copies (Pharmacokinetics)	PBMC	X		X		X			X	X		X		X	X	X	X	X	X	
Cytokine Analyses[5]	Serum	X	X	X	X	X	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	X	
CCI	Serum		X											X		X	X	Week 12, Week 24	X	
Liquid biopsy (blood)[6]	Whole blood	X							X					X	X	X		X	X	
Tumor Biopsy[7]	Biopsy	X[8]													X[9]			X[10]		

1. All assessments need to be performed at all visits specified in the Table, up to and including the visit establishing confirmed PD or study withdrawal or discontinuation. There are no assessments that need to be performed at Weeks 5, 7, and 10; therefore, Weeks 5, 7, and 10 are not present in this Table.
2. See Section 5.3.1 of this substudy for the definition of the end of Interventional phase.
3. Baseline assessments will be performed until Day -8.
4. All assessments to be performed prior to T-cell infusions.
5. If CRS is suspected, cytokine samples should be collected every day for the first week and approximately every other day thereafter until symptoms are improving or an alternative diagnosis is confirmed.
   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 3 footnote 20). In addition, troponin, and N-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests should be monitored for participants with CRS Grade ≥2 as clinically indicated.

6. Blood sample from which circulating cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes may be extracted should match tumor biopsy visits and imaging (Body CT/MRI) visits as well as be taken on Day 8 and Day 22.
7. 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 if clinically indicated.
8. 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). For participants who already provided a fresh screening biopsy and did not receive any subsequent bridging or standard of care anti-cancer therapy, this may be used as the Baseline sample if obtained preferably within 90 days prior to initiating lymphodepleting chemotherapy.
9. Week 4 biopsy must be taken preferably between Days 21-23 if medically feasible, but window for collection is extended until Week 6 visit (Day 39).
10. Must be taken once at confirmed disease progression if medically feasible.

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

Table 6 Substudy 1 Schedule of Activities – Follow-up after Disease Progression or after Completion of Interventional Phase Follow-up

Substudy 1: Follow-up after Disease Progression or after Completion of Interventional Phase Follow-up[1]												
Time post GSK3901961 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 [redacted] for safety[8,9]		X	X	X	X	X	X	X	X	X	X	X[7]
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. Participants will continue with all interventional phase assessments until disease progression when they will transfer to the follow-up portion of the study. To ensure adequate collection of safety information, participants must remain in the interventional portion of the study for at least 90 days post T-cell infusion.
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 annual follow-up between years 6-15, all SAEs and all delayed AEs will be recorded in the CRF if reported by the participant 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 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, samples for CCI and persistence of gene modified cells will be discontinued (Section 9.1.12 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.

IEC = Institutional ethics committee; IRB = Institutional review board; CCI ; CCI

3 INTRODUCTION

3.1 Background and Rationale

Core Protocol Section 3.1 describes the rationale for investigating second generation T-cell therapy. Core Protocol Section 3.2 provides background information on TCR approach, NYESO1, and GSK3377794 (letetresgene autoleucel, lete-cel).

The background and rationale for investigating the specific second generation product, GSK3901961, in SS/ myxoid/round cell liposarcoma (MRCLS) and NSCLC is provided in this section.

3.1.1 GSK3901961

GSK3901961 consists of autologous CD4+ and CD8+ NYESO1 TCR engineered T cells that have been modified to co-express the human CD8α chain using multicomponent engineering. This is, therefore, a second-generation T-cell therapy product based on GSK3377794 (lete-cel), and both products express the identical affinity-enhanced NYESO1/LAGE1a specific TCR. CD8 co-receptor is needed to establish a stable binding with the peptide and HLA-A*02 complex for optimal signaling especially in situation of low antigen expression levels. Indeed, CD4+ T cells that lack CD8 co-receptor expression, have approximately 10-fold lower tumor cell binding potential than CD8+ T cells expressing the same HLA class I restricted TCR.

Co-expression of CD8α by GSK3901961 resulted in enhanced proliferation and target engagement of its CD4+ cell population in vitro. Upregulation of CD4-specific surface markers, cytokines and chemokines compared to first generation GSK3377794 indicate improvement of CD4 helper functions, potentially leading to and enhanced overall anti-tumor response. Pre-clinical assessment of GSK3901961 is described in the IB [GlaxoSmithKline Document Number RPS-CLIN-015261].

Increased activation of tumor-specific CD4+ helper T cells enhances stimulation of tumor-specific effector T cells, recruits other immune cells to the tumor site and is therefore expected to result in an enhanced anti-tumor immune response.

Efficacy enhancement of tumor-specific autologous T cells by co-expression of human CD8α is currently being evaluated in the Adaptimmune SURPASS trials of ADPA2M4CD8 (NCT04044859, NCT04752358). This asset, which consists of MAGE-A4-specific affinity-enhanced TCR T cells that also co-express CD8α, has been tested in 25 patients with a wide variety of solid cancers. Twenty-two patients were evaluable for response at data cutoff of 02 August 2021. The study results showed an 86% overall disease control rate and a 36% overall response rate, including 1 complete response and 7 partial responses (Hong 2021).

3.1.2 Synovial Sarcoma

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.

SS is a rare malignancy accounting for approximately 5–10% of all STS [Riedel, 2018; Noone, 2018; Brennan, 2016; Honoré, 2015]. The estimated incidence of SS is 0.15 per 100,000 in the United States (U.S.) and 0.14 per 100,000 in the UK [Wang, 2017; Stacchiotti, 2018; Brennan, 2016].

SS 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 localized 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 SS will develop metastatic disease [Ten Heuvel, 2009; Krieg, 2011], and the survival for patients developing metastatic disease is approximately 12-15 months. These rates have not improved over the last 2 decades.

Standard first-line treatment in patients with advanced, unresectable, or metastatic SS consists of anthracycline chemotherapy as single agent or as part of combination regimens (e.g., doxorubicin with ifosfamide), which induces responses in 18-30% [Spurrell, 2005; Sleijfer, 2010; Vlenterie, 2016]. Dacarbazine is also authorized 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].

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 authorized by EMA and by FDA for treatment of patients with metastatic STS who have failed prior chemotherapy. However, response rates in SS 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 U.S. 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 SS patients, in a Phase 2 study, SS 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.

It has been recognized that a proportion of patients with soft tissue sarcomas, and up to 76% of SS, express high levels of the cancer testis antigen NY-ESO-1 [Lai, 2012] and GSK3377794 (lete-cel) has demonstrated clinical activity in SS (See Section 3.2 of this Substudy). This warrants investigation in SS.

3.1.3 Myxoid/Round Cell Liposarcoma (MRCLS)

Liposarcomas (LPS) are the most common type of STS in adults and, as such, arise from mesenchymal cells and express adipose features [Moreau, 2012; Haniball, 2011]. MRCLS is the second-most common histologic subtype-comprised of both myxoid liposarcoma (MLS) and round cell liposarcoma (RCLS)-with the chromosomal translocation t(12;16)(q13;q11) found in >90% of tumors [Moreau, 2012; Haniball, 2011; Manji, 2016]. RCLS is a poorly differentiated, high-grade variant of MLS defined by >5% round cell component in the tumor [Moreau, 2012; Smith, 1996; Fiore , 2007]. In a retrospective study comparing MLS and RCLS in 29 patients, MLS was generally found to be low-grade and responds well to chemotherapy [Amer, 2020]. Whereas, RCLS is usually more aggressive, has higher rates of metastasis, poorer prognosis, and a poorer response to chemotherapy relative to MLS, though response to chemotherapy is better overall compared to other STS histologic subtypes [Amer, 2020; Smith,1996; Fiore , 2007].

MRCLS accounts for approximately 40% of LPS and 10% of all STS [Pollack, 2012]. MRCLS is a rare disease with an incidence rate of approximately 0.21 per 100,000 [Bock, 2020].

Predicting MRCLS prognosis is challenging in that tumor site, grade, depth, necrosis, and potentially patient age are used to determine outcome at the time of diagnosis [Moreau, 2012; Haniball, 2011]. Unlike most sarcomas, MRCLS has a propensity for extrapulmonary metastasis to soft tissue and bone, occurring in 14-38% of patients [Moreau, 2012; Gouin, 2019]. Consequently, metastases during staging and follow-up are sometimes missed [Moreau, 2012]. In general, the 5-year overall survival is 76.4-91% for MLS and 54.9-79% for RCLS [Moreau, 2012; Amer, 2020]. However, diagnosis of bone metastases is an indicator of poor survival, which is reflected in the drastic decline of the 5-year overall survival to 16%, with median survival ranging from 8.5 to 21.9 months indicating metastatic MRCLS is a life-threatening disease [Gouin, 2019].

Patients with locally recurrent, unresectable, or metastatic disease are treated with chemotherapy [Amankwah, 2013]. First-line therapy utilizes an anthracycline-based regimen (i.e., doxorubicin either as a monotherapy or in combination with ifosfamide) and has a 48% response to treatment [Manji, 2016; Amankwah, 2013]. Both trabectedin and eribulin are approved for use in patients treated with a prior anthracycline-containing regimen [Manji, 2016]. Trabectedin demonstrates a median PFS of 5.6 months in MRCLS and eribulin has a median OS of 13.5 months for all LPS [Manji, 2016].

Given the lack of treatment options and low response rates in unresectable/metastatic disease, there is a clear unmet medical need. Furthermore, in one study evaluating NYESO1 expression in MRCLS, 100% stained positive for NY-ESO-1, with 23 of the 25 samples staining at least 2+ [Pollack, 2012]. This indicates that MRCLS patients may be good candidates for NY-ESO-1 TCR T cells.

3.1.4 Non-Small Cell Lung Cancer

Lung cancer is the most common cause of cancer death, accounting for 1.76 million deaths worldwide [WHO, 2018]. Although the incidence and mortality rates attributed to

cancer vary across regions globally, lung cancer remains the leading cause of cancer death in men and the second leading cause of cancer death in women [Torre, 2015]. Non-small cell lung cancer accounts for the majority of lung cancer cases (up to 85%) with disease stage, histological subtype (viz., adenocarcinoma, squamous, and large cell) and molecular features playing the principal role in the selection of the course of treatment.

In metastatic NSCLC that is positive for a specific molecular alteration (e.g., epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], c-ros oncogene 1 [ROS1], BRAF), targeted single-agent approaches are recommended [NCCN, 2017; Postmus, 2017]. For patients with metastatic non-squamous NSCLC who present with wild-type (WT) disease, the incorporation of an anti-PD-1/PD-L1 inhibitor, either alone or in combination with platinum-based chemotherapy is administered as first-line treatment (Melosky, 2020). Subsequent-line treatment options include other single-agent anti-PD-1/PD-L1 inhibitors (e.g., nivolumab, atezolizumab) if not administered in the first line [Brahmer, 2015; Rittmeyer, 2017] or platinum-based chemotherapy if not administered in the first line. Older therapies, such as pemetrexed for non-squamous NSCLC (if not used as part of the platinum-based chemotherapy doublet), gemcitabine for squamous NSCLC, or docetaxel for all NSCLC sub-types have been relegated to later lines and can be selected, based on a patient's treatment history, disease characteristics, and performance status. The clinical activity of older single-agent chemotherapies, such as docetaxel for second-line treatment in NSCLC, is limited with response rates in the range of 9% to 24% [Shepherd, 2000; Hanna, 2004].

Approximately 11% to 43% of NSCLC tumors express NY-ESO-1 [Grah, 2008; Gure, 2005]. The Cancer Genome Atlas Ribonucleic Acid (TCGA RNA) sequencing database indicates the following frequency of expression of NY-ESO-1 and LAGE-1a, respectively: 12% and 8.5% in lung adenocarcinoma and 26% and 21% in squamous cell carcinoma. GSK3377794 has been investigated in NSCLC in two studies (208471and 208749).

3.2 Benefit/Risk Assessment

3.2.1 Risk Assessment

GSK3901961 has not been tested in humans prior to this study; therefore, the known safety profile of this IP comes primarily from the nonclinical information obtained to date (see GSK3901961 IB [GlaxoSmithKline Document Number RPS-CLIN-015261]) and the safety profile of GSK3377794 (letetresgene autoleucel, lete-cel).

Clinical Safety Profile of GSK3377794 (lete-cel)

The known safety profile of GSK3377794 (lete-cel) is based on 166 enrolled and 125 treated participants as of 27 January 2021 (see GSK3377794 IB [GlaxoSmithKline Document Number RPS-CLIN-015027]). The most commonly reported treatment emergent adverse events which occurred in ≥50% of participants following lymphodepleting chemotherapy and GSK3377794 (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 ≥50% of participants following lymphodepleting chemotherapy and GSK3377794 (lete-cel) infusion were leukopenia/WBC decreased (78%), neutropenia/neutrophil count decreased (74%), thrombocytopenia/platelet count decreased (62%), anemia/RBC decreased (58%), and lymphopenia/lymphocyte count decreased (52%). These AEs are consistent with expected immediate adverse events after lymphodepletion chemotherapy. These events are also consistent with those observed after the first infusion with lete-cel.

Across all studies, 47 (38%) participants had SAEs considered by the Investigator to be related to study treatment. The most common treatment-related SAEs occurring in more than 2 subjects were as follows: CRS (15%), pyrexia (6%), neutropenia/neutrophil count decreased (5%), rash/rash maculo-papular (4%), thrombocytopenia/platelet count decreased (4%), and febrile neutropenia (3%).

Among the adverse events of special interest are the following:

- CRS was reported in 52 cases (of 125) as of 27 January 2021 across all GSK3377794 (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. Twelve cases were treated with tocilizumab. Median duration of all CRS events was 8-9 days (range 1-28 days).
- 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.
- Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported as an SAE in 1 case with multiple brain metastasis; this case was transient and resolved in 2 days with supportive care. A second case of ICANS (Grade 1) was reported for a second participant. This second case was not serious and resolved after 2 days.
- Five (4%) participants had reported treatment-emergent AE of pancytopenia (5 participants: 3 with Grade 4 and 1 with Grade 3) or bone marrow failure (2 participants: 1 with Grade 5 fatal and 1 with Grade 3).
- GBS has been reported in 2 participants, both of which completely recovered with standard immune-globulin treatment.

To date, none of the analyses for PPD and PPD are positive for PPD or PPD.

Non-Clinical Safety Profile of GSK3901961

Because of the human specificity, standard toxicology studies cannot be conducted. GSK3901961 demonstrated the same potent activity against NY-ESO-1 or LAGE-1a expressing tumor cell lines as observed with GSK3377794 (lete-cel), with no relevant

off-target responses noted (see GSK3901961 IB [GlaxoSmithKline Document Number RPS-CLIN-015261]). However, weak normal cell recognition response (IFNγ release) was detected against one tonsil cell line, one liver stellate, and one activated B cell line. These weak responses were subsequently shown to be due to recognition of low levels of target antigen or unidentified EBV peptides. Of note, a similar weak response with the same cell line was noted with GSK3377794 (investigated in ongoing clinical trials). In clinical studies with GSK3377794 (lete-cel), there are no findings indicative of GSK3377794 recognition and engagement with these cell types.

No changes in cytokine levels, indicative of acute cytokine release following infusion of GSK3901961 were observed in the in vitro whole blood assay. The in vitro alanine scan and cellular assay 'X-scan' (amino acid scanning enabling the determination of peptide residues critical for TCR engagement) assays did not identify any potential off target cross reactivity that would be indicative of potential safety concern in the proposed clinical trials. Finally, the in vitro alloreactivity assays showed that GSK3901961 did not recognize a different peptide on another HLA class I allele. Furthermore, the findings in this in vitro nonclinical safety package are comparable to those noted with GSK3377794 (lete-cel).

The potential for carcinogenicity of TCR therapies is considered low because terminally differentiated cells are transduced (rather than pluripotent T cells) and the persistence of the transduced cells is unlikely to be durable [Conlon, 2018]. Additional safety modifications in the vectors used to generate GSK3901961 include SIN LTR sequences and an internal human housekeeping gene (EF-1α) promoter, so the vector does not contain enhancer elements that were linked to transactivation of oncogenes in early (γretroviral- vector mediated) gene therapy clinical trials [Hacein Bey-Abina, 2008].

The risk of potential for on- or off-target recognition and engagement on peripheral nerves is low based on lack of NY-ESO-1 and LAGE-1a mRNA expression, NY-ESO-1 protein expression and the reported absence of HLA expression by normal Schwann cells and neurons. Pre-clinical assessment of GSK3901961 is described in the IB [GlaxoSmithKline Document Number RPS-CLIN-015261].

Table 7 Risk Mitigation Strategy

Potential Risk of Clinical Significance	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 • Hyponatremia • Neurotoxicity	Cases were reported with both drugs.	Please refer to the prescribing information of fludarabine and cyclophosphamide and Core Section 12.7.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Visual impairment • Peripheral neuropathy	Cases were reported with fludarabine	Please refer to the prescribing information of fludarabine.
IP GSK3901961		
Fatal cardiac arrest	Potential risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been 2 reports of unexpected cardiac arrest. The first occurred 5 months after T-cell infusion and was confounded by hypotension due to poor oral intake and concurrent renal insufficiency. The second occurred approximately 1 week after T-cell infusion in the setting of a recent fungal catheter line infection, concurrent treatment with caspofungin and multifocal pneumonia / edema seen on chest CT.	Participants with significant cardiac risk factors or with CRS ≥ Grade 2 will receive close cardiac monitoring (Core Sections 9.1.6 and 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 9.1.7). Central lines should be closely monitored for infection (Core Section 12.7.2). Systemic fungal infections are excluded (Exclusions 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 an adverse event of special interest (AESI)	I/E criteria exclude participants with pre-existing autoimmune disorders (Section 6.2). See management for CRS, Core Section 12.7.5). Events Grade ≥3 must be reported as SAEs and submitted to GSK within 24 hours.
Graft vs. Host disease (GVHD)	Identified risk associated with TCR T cells reacting against normal tissues and organs, considered an AESI	I/E criteria exclude participants with pre-existing autoimmune disorders (Section 6.2). See management for GVHD, (Core Section 12.7.6)
Hematopoietic cytopenias (including Pancytopenia with bone marrow failure/Aplastic Anemia)	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion, considered an AESI	I/E criteria exclude participants with hematologic imbalance. See management for pancytopenia, Core Section 12.7.7
Hemorrhage 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 Core Section 12.7.3
Hypersensitivity	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion, considered an AESI	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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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.
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 9.2.7).
Visual impairment	Potential risk: There was a report of decreased vision in a participant who received TCR-T 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 GSK3377794 (lete-cel) developed GBS.	Participants with prior or active demyelinating disease will be excluded (Section 6.2). Neurologic consultation is required for

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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 enrolment 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)	Theoretical 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 ICAN are excluded (Section 6.2). Monitoring criteria for ICAN are described in Core Section 12.7.8.
CCI [redacted]		
Risk to Females of Reproductive Potential	Safety during pregnancy has not been established. It is not known whether antigens are excreted in human milk and safety during lactation has not been established. Participants who are pregnant, intending to become pregnant, or are breastfeeding are excluded from TCR-T studies. Preclinical reproductive toxicity studies were not conducted because of the human specificity of TCR therapy.	Pregnant and breastfeeding women are excluded from study participation. Study incorporate specific contraception requirements for male and female participants Pregnancy testing is conducted during participation in the study.
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 of the Core Protocol).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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.

3.2.2 Benefit Assessment

No clinical studies have been conducted to date with GSK3901961. The clinical benefit expected from this IP is based on the clinical benefit observed with GSK3377794 (lete-cel) and on the considerations of additional advantages provided by the multi-component engineering.

As of 27 January 2021, 125 participants have been treated with GSK3377794. Objective responses have been observed in the completed SS study (208466/ADP-04511) and in multiple myeloma post-autologous transplant study (209393/ADP-01411). In Cohort 1 of study 208466 (which is similar to the treatment regimen proposed for this protocol), a single infusion of GSK3377794 (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 SS.

Objective responses have been observed in 21 (84%) out of 25 of participants in multiple myeloma after autologous transplant (study 209393/ADP-01411) [GlaxoSmithKline Document Number 2018N369930_02].

Additionally, studies conducted by the NCI Surgery Branch have demonstrated that adoptive immunotherapy using T cells genetically engineered to recognize NYESO1 following lymphodepletion led to objective antitumor responses in 4 of 6 patients (67%) [Robbins, 2011] and 11 of 18 patients (61%) [Robbins, 2015] with SS. The estimated overall three and five-year survival rates for these patients with SS 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, 2021]. Nine of 10 patients in Cohort 2 experienced tumor shrinkage, and 4 of these 10 patients had a confirmed partial response. These collective results thereby demonstrated encouraging clinical activity of GSK3377794 across multiple NY-ESO-1 expressing tumor types.

3.2.3 Overall Benefit: Risk Conclusion

GSK3901961 has not been tested in humans prior to this study. Clinical data initially demonstrate the safety and activity of the related product GSK3377794 (lete-cel). The

typical risks associated with T-cell therapies such as CRS and neurotoxicity (ICANS) have been observed in 42%and 1% of 125 patients treated, respectively, and resolved with appropriate management (see GSK3377794 IB [GlaxoSmithKline Document Number RPS-CLIN-015027]). As GSK3901961 has the same target as GSK3377794 (letecel), their TCR related safety profile is expected to be similar and acceptable. Any additional safety events related to multi-component engineering will be monitored and managed in this study; some potential events are also incorporated in the DLT criteria. Additionally, the pre-clinical data support target specificity of GSK3901961.

From the benefit standpoint, enhanced efficacy over GSK3377794 (lete-cel) is expected as a result of enhanced binding and functional activity of CD8α co-expressing NY-ESO-1 T cells. In view of the clinical responses observed with lete-cel in relapsed, refractory patients, and as per the risk assessment presented above, the benefit / risk ratio supports a FTIH clinical investigation of GSK3901961 in participants with relapsed refractory advanced and metastatic solid tumors. NSCLC and SS / MRCLS.

4 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the safety, tolerability and determine recommended Phase 2 dose (RP2D) of GSK3901961 in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive participants with: - NY-ESO-1 and/or LAGE-1a positive previously treated metastatic NSCLC (Cohort 1) - NY-ESO-1 and/or LAGE-1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2)	• Frequency of dose-limiting toxicities (DLTs) • Frequency and severity of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESI; as defined in the core protocol)
Secondary - Efficacy	
To investigate the anti-tumor activity of GSK3901961 in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive participants with: - NY-ESO-1 and/or LAGE-1a positive previously treated metastatic NSCLC (Cohort 1) - NYESO1 and/or LAGE1a positive, previously treated, advanced (metastatic or unresectable) SS/MRCLS (Cohort 2)	• Overall Response Rate (ORR) (investigator assessed according to RECIST v1.1) • Duration of Response (DoR)
Secondary - Pharmacokinetics	
To characterize in vivo cellular PK profile (levels, expansion, persistence) of GSK3901961 over time	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit

Objectives	Endpoints
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI	

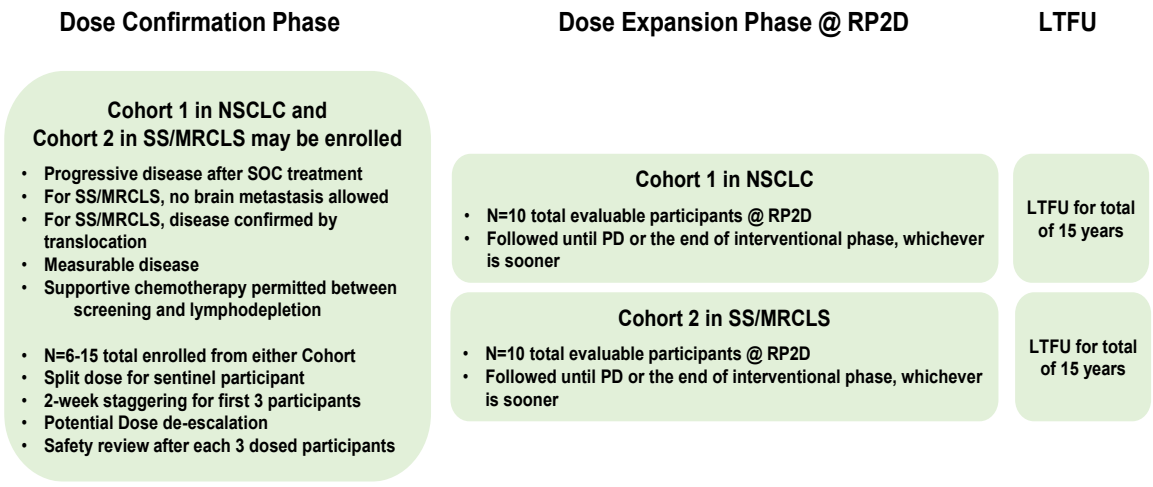
AE = adverse event/s; AESI = adverse event/s of special interest; AUC (0-t) = area under the time curve from zero to time t; Cmax = maximum concentration; CRS = Cytokine Release Syndrome; DLTs = dose-limiting toxicities; DNA = deoxyribonucleic acid ; DOR = duration of response; ECG = Electrocardiogram; CCI ; HLA = human leukocyte antigen; CCI ; MRCLS = myxoid/round cell liposarcoma; NSCLC = non-small cell lung cancer; NYESO1 = New York esophageal antigen-1; ORR = overall response rate; CCI ; CCI ; CCI ; RECIST = Response Evaluation Criteria In Solid Tumors; RNA = ribonucleic acid; RP2D = recommended phase 2 dose; SAE = serious adverse event; SS = synovial sarcoma; Tmax = Time to Cmax; CCI ; CCI

5 SUBSTUDY DESIGN

5.1 Overall Design

This is a first time in human (FTIH) multi-cohort, non-randomized, open-label substudy to investigate GSK3901961 in previously treated participants with advanced (metastatic or unresectable) SS /MRCLS or previously treated metastatic NSCLC. This substudy will consist of two phases: Dose Confirmation Phase and Dose Expansion Phase (Figure 1).

Figure 1 Substudy 1 Design



NOTE: Participants included in different substudies may have the same eligibility criteria. Sponsor will inform Investigators of the participant assignments between substudies and indicate if the participant is a sentinel participant and the number of remaining slots.

LTFU = long-term follow-up; MRCLS = myxoid/round cell liposarcoma; NSCLC = non-small cell lung cancer; PD = progressive disease; RP2D = recommended phase 2 dose; SS = synovial sarcoma.

5.1.1 Dose Confirmation Phase

Dose confirmation phase will commence first and within this phase, participants will be assigned to one of two cohorts:

- Cohort 1 - GSK3901961 in previously treated metastatic NSCLC
- Cohort 2 - GSK3901961 in previously treated advanced (metastatic or unresectable) SS or MRCLS.

NSCLC or SS / MRCLS participants may be enrolled within this phase, based on competitive enrollment. Sponsor will inform Investigators of the participant assignments within this phase and indicate if the participant is a sentinel participant (see Core protocol Section 8.1.2 for definition) and the number of remaining slots for dose confirmation phase. Once all participants needed for dose confirmation (n=6–15) have been assigned, participants will be assigned to dose expansion phase.

The primary objective of the dose confirmation phase is to identify the recommended phase 2 dose (RP2D) of GSK3901961. RP2D will be determined as the maximum tolerated dose (MTD) or lower that provides adequate biologic activity with superior tolerability. The MTD is defined as the dose that maximizes the probability of target toxicity of 30% while controlling the probability of excessive or unacceptable toxicity.

The Dose Selection Committee review will occur after the DLT period in every 3 participants with either SS/MRCLS or NSCLC, to enable dose decision until the final dose selection is achieved (6 to 15 participants).

The starting dose will be the RP2D of GSK3377794 (lete-cel); that is, the initial group of 3 participants will receive a dose in the range of 1×10^9 − 8×10^9 transduced T cells. If DLTs are reported that require dose de-escalation- according to the modified toxicity probability interval 2 (mTPI-2) model, then a lower dose range of 0.1×10^9 − 0.8×10^9 transduced T cells will be explored, with the possibility to re-escalate if the model supports such action. Alternative doses may be investigated if warranted by the emerging safety profile.

5.1.1.1 Split Dosing and Staggered Treatment

The first study participant receiving GSK3901961 (SS/MRCLS or NSCLC) will receive the total assigned dose (1×10^9 − 8×10^9 transduced T cells) as 2 separate infusions, 7 days apart, in aliquots of ~30% (first infusion) and ~70% (second infusion) of the total manufactured dose, respectively. After the first infusion, participant will remain hospitalized for 7 days and be monitored per SOA. If no dose-limiting toxicities (DLTs defined in Section 8.2 of the Core Protocol) are reported during this time, participant will receive the second dose and be hospitalized for an additional 3 days. If no DLTs are reported for the participant receiving split dosing during the stagger period defined in the next paragraph, then all subsequent participants treated with the particular investigational agent will receive the full dose as a single, i.e. one-time, infusion. If DLTs are reported for the participants receiving split doses, additional participants may be treated with a split dose regimen at the discretion of the sponsor in consultation with the participating Investigators and the DSC.

At each dose level, dose administration in the first 3 participants will be staggered. Initiation of the lymphodepleting regimen in the 2nd and 3rd participant (across SS/MRCLS and NSCLC) will be separated by a minimum of 2 weeks from the complete dose administered to the prior participant to enable close monitoring of toxicities in each participant and DSC consultation if needed. Once the first 3 participants have received the dose successfully per DSC agreement, subsequent participants will receive lymphodepletion and the IP without any delays.

5.1.1.2 Determining the RP2D

To find the RP2D, modified toxicity probability interval 2 (mTPI-2) design will be implemented (Table 8) [Guo, 2017]. Participants with SS/MRCLS or NSCLC will be recruited and treated in blocks of three.

The design aims to identify a dose with a true underlying toxicity rate of 30%, with a range of 25% to 35%. The monitoring rules guiding dose escalation are provided in Table 8. Columns provide the numbers of participants treated at the current dose level, and rows provide the corresponding numbers of participants experiencing DLTs. The entries of the table are dose-finding decisions (i.e., R, S, and D) representing re-escalating the dose, staying at the same dose, and de-escalating the dose. In addition, decision U means that the current dose level is unacceptable because of high toxicity and should be excluded from the trial. For example, when one of three participants experiences toxicity, the decision can be located at row 1 and column 3, which is S –to stay at the current dose level. Consequently, the next block of participants will be treated at the same dose level

currently being used. If zero of three participants experience toxicity, the decision is at row 0 and column 3, which is R –to re-escalate. Thus, the next block of participants will be treated at the higher dose level, if available. If three of three participants experience toxicity, the decision is U –to de-escalate to the lower dose level and exclude the current dose from the trial, because the toxicity level is unacceptable.

The final determination of RP2D will be based on the mTPI-2 recommended dose, as defined as ≥6 participants treated at this dose and an observed toxicity rate closest to the targeted toxicity rate at 30% after isotonic regression, in addition to considering the clinical response rate and available PK and PD data generated from all participants.

Table 8 DLT De-Escalation/Re-Escalation Rules

		Number of participants who received study drug at the current dose				
Number of participants with Dose Limiting Toxicities (DLTs) at the current dose		3	6	9	12	15
	0	R	R	R	R	R
	1	S	R	R	R	R
	2	D	S	R	R	R
	3	U	D	S	S	R
	4		U	D	S	S
	5		U	U	D	S
	6		U	U	D	D
	7			U	U	D
	8			U	U	U
	9			U	U	U
	10				U	U
	11				U	U
	12				U	U
	13					U
	14					U
	15					U

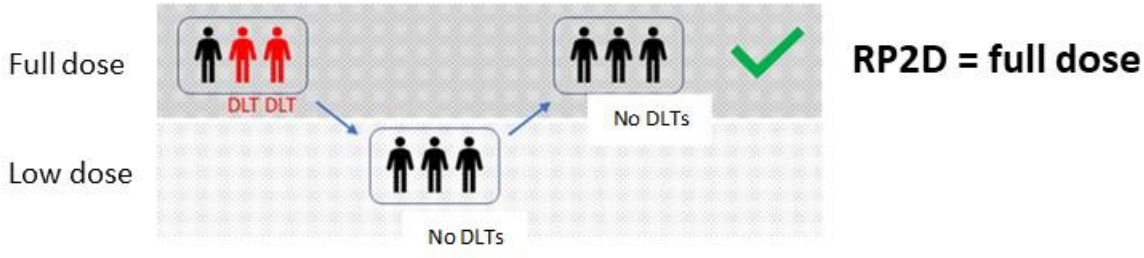
R=Re-escalate to the higher dose if applicable OR Stay at the current dose otherwise.
S=Stay at the current dose.
D=De-escalate to the lower dose if applicable OR Stay at the current dose otherwise.
U=The current dose is unacceptably toxic; de-escalate to the lower dose if applicable.

MTD=30%
Epsilon1=Epsilon2=0.05

For example, in the scenario depicted in Figure 2 below, if there are 2 participants with DLTs out of the first 3 dosed at the full dose of $1 \times 10^9 - 8 \times 10^9$ transduced cells, the dose will be de-escalated and the next 3 participants will be treated at the reduced dose of $0.1 \times 10^9 - 0.8 \times 10^9$ transduced cells. At the low dose, if there are 0 participants with DLT out of 3 participants, the dose will be re-escalate and the next 3 participants will be

treated at the full dose. If 0 participants have DLTs out of these 3 additional participants, the full lete-cel dose will be suggested as the RP2D for GSK3901961.

Figure 2 Example of Dose De-Escalation/Re-Escalation



Dose de-escalation or RP2D confirmation decision will be made by the DSC based on all available clinical safety data as well as any other data that might inform the dose selection process, and select CCI and PK data, if available. The DLT information on all participants enrolled in the trial will be used to update the estimated dose toxicity relationship and provide supportive information in addition to the mTPI-2 model design in the next escalation/de-escalation decision; the mTPI-2 approach is expected to be used as the primary criterion for dose confirmation.

5.1.2 Dose Expansion Phase

After RP2D has been determined, the dose expansion phase will begin.

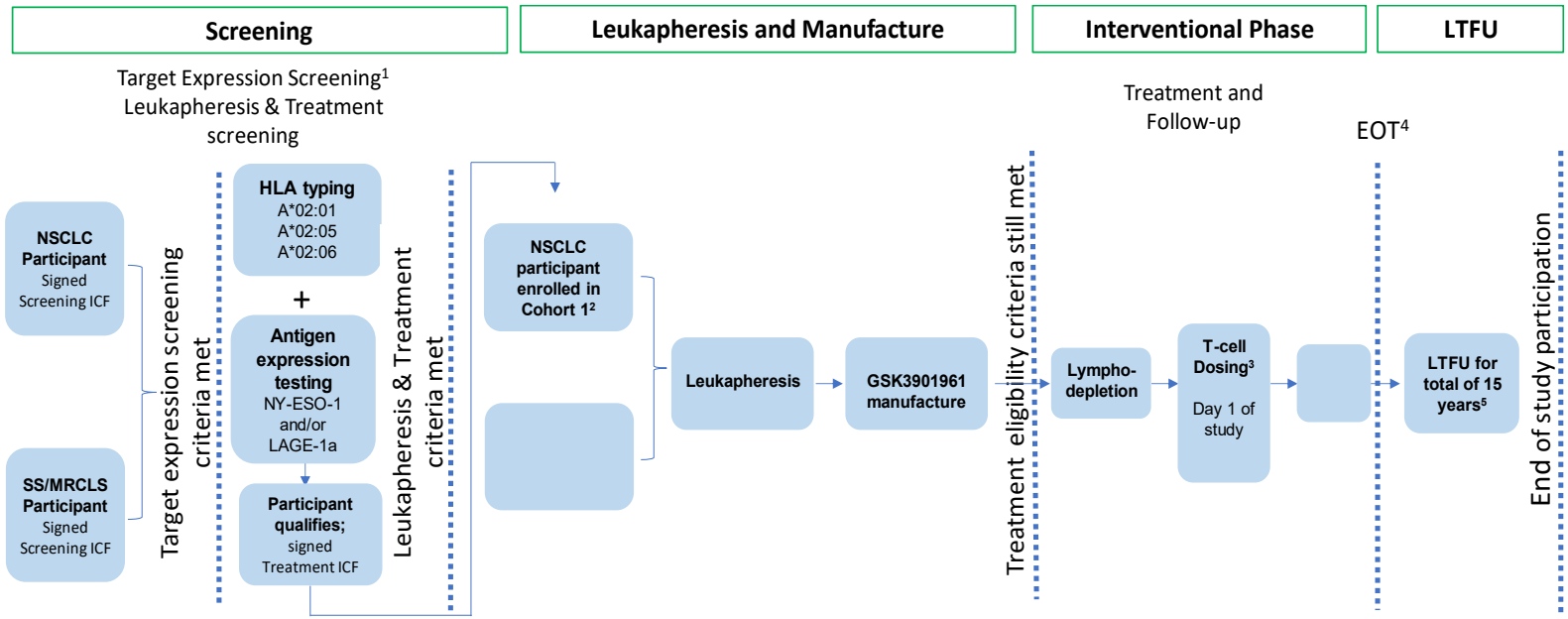
Each cohort will enroll additional participants to ensure n=10 participants have become evaluable at the RP2D in each cohort. Evaluable participants are those who have received T-cell infusion and have completed at least 2 post Baseline disease assessments since infusion or have progressed or died or were withdrawn from the substudy.

If supported by safety and efficacy results, additional participants may be enrolled to confirm the safety and efficacy via a protocol amendment or as part of a separate protocol. For Cohort 1, two or more confirmed responses (CR or PR) out of 10 evaluable participants treated at RP2D may provide enough efficacy evidence to enroll additional participants. For Cohort 2, five or more confirmed responses (CR or PR) out of 10 evaluable participants treated at RP2D may provide sufficient efficacy evidence to expand and enroll additional participants. This will serve as guidance for final decisions regarding enrollment of additional participants, which will be based on a review of the totality of the data. Additional details will be provided in the SAP.

5.1.3 Participant Journey

For each individual participant, the study will consist of the following (Figure 3): Screening; leukapheresis and manufacture; interventional phase; and LTFU.

Figure 3 Participant Journey



1. Screening, including HLA typing and antigen testing, may be done in this study or as part of a separate Pre-screening protocol.
2. Sponsor will inform Investigators of the participant assignments between substudies and indicate if the participant is a sentinel participant and the number of remaining slots.
3. The first participant to be dosed will receive the total dose in 2 separate infusions as aliquots of ~30% and ~70% of the total manufactured dose, administered 7 days apart. The second infusion will only be administered if no acute toxicities preventing full dosing are observed. If no DLTs are reported for the participants receiving split doses, then all subsequent participants administered the particular product will receive the full dose as a single, i.e. one-time, infusion.
4. See Section 5.3.1 of this substudy for definition of the end of interventional phase for a participant.
5. The LTFU assessments and procedures may be done in this study or under a separate LTFU protocol.

EOT = end of treatment (i.e., interventional) portion of the trial; HLA = human leukocyte antigen; ICF = informed consent form; LTFU = long-term follow-up; MRCLS = myxoid/round cell liposarcoma; NSCLC = non-small cell lung cancer; SS = synovial sarcoma.

Screening

See inclusion / exclusion criteria in Section 6 of this Substudy for complete details of Screening approach.

This study will enroll participants with previously treated advanced (metastatic or unresectable) SS / MRCLS or NSCLC.

Target expression Screening will be conducted in participants who have evidence of advanced disease and may still be undergoing a prior line of therapy.

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. Central laboratory HLA typing is frequently performed first, followed by tumor antigen expression testing (considering the expected >50% attrition with HLA). This testing may also be performed in parallel. If an Investigator is aware of a participant's positive HLA status (the presence of HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 based on high resolution local testing) the Investigator may provide tumor tissue for antigen testing either at the same time as or before a confirmatory HLA test by the central laboratory. The use of the HLA and the NY-ESO-1 and/or LAGE-1a tests in this substudy is investigational.

NOTE: target expression Screening may also be performed under a separate Screening protocol such as the GSK molecular disease characterization initiative (MDCI) study (213299), or under other NYESO1/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 eligibility within 28 days prior to the day of the scheduled leukapheresis procedure.

Leukapheresis and Manufacture

Eligible participants will be entered into one of the two study cohorts one in NSCLC and one in SS / MRCLS. Leukapheresis procedure requires that participant has completed prior line of therapy and has radiographic or clinical evidence of disease progression.

Once entered into the appropriate cohort, participants will undergo leukapheresis.

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

See Section 5.2 in the Core Protocol and Section 7.1.2 of this Substudy for supportive chemo- or radio-therapy administration.

Interventional Phase

See Section 5.2 Part 3 in the Core Protocol. T-cell administration will be performed as follows.

GSK3901961 will be administered as an intravenous (IV) infusion on Day 1. There is no Day 0 in this study. All non-sentinel participants will be admitted into the hospital on the day of T-cell infusion and will be hospitalized for at least 3 days post T-cell infusion. After hospital discharge, participants will maintain close follow up with the Investigator for the remaining 2 weeks after T-cell infusion. The first study participant receiving GSK3901961 (sentinel participant) will receive full dose range as 2 separate infusions and will be hospitalized for a minimum of 10 days post first T-cell dose infusion (as described in Section 5.1.1 of this Substudy), then closely monitored by the Investigator for the remaining of 2 weeks after T-cell infusion.

Following T-cell infusion, participants will be monitored until one of the following occurs, whichever is sooner:

- Confirmed disease progression;
- Death;
- End of interventional phase (see Section 5.3.2 of this substudy).

LTFU

See Section 5.2 Part 4: Long-Term Follow-Up (LTFU) of the Core Protocol.

5.1.4 Tumor Biopsies

A fresh biopsy or archival tumor FFPE from representative tissue is required from all participants to be used for antigen expression eligibility screening. If fresh biopsy is performed, then this tissue should be used. If multiple archival samples are available, then the most recent archival sample should be used. For synovial sarcoma and MRCLS archival samples, no more than 5 years may have elapsed from date of collection to date of target expression screening. For NSCLC, no more than 2 years may have elapsed from date of collection to date of target expression screening.

a. Formalin-fixed paraffin embedded (FFPE) tumor specimens in paraffin blocks are preferred. Twenty unstained slides (5-micron serial fresh cut) are requested as an alternative (see Laboratory Manual for details)

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 pleural effusion, bone metastases, and lavages are not acceptable

d. Tissue should be sent to the central testing laboratory within 1 year of the participant signing the target screening consent and must be of good quality on the basis of total and viable tumor cells

A pre-treatment Baseline tumor sample collected within 28 days prior to initiating lymphodepletion is required for Substudy 1. This tumor sample will be used as the

Baseline for [redacted] 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 screening and did not receive any subsequent bridging or standard of care anti-cancer therapy, this screening biopsy may be used as the Baseline sample if the screening biopsy was obtained preferably within 90 days prior to initiating lymphodepleting chemotherapy.

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 may be obtained at any time during the study execution.

Refer to Core Section 9.10.1 and the SRM for additional details for tumor biopsies.

5.2 Number of Participants

Up to 10 evaluable participants treated with RP2D are needed per cohort for a total of 20. Up to 9 additional participants (shared between the cohorts) may be needed during the dose confirmation phase to determine RP2D. Thus, the total expected maximal number of participants is approximately 29.

Any participant who does not receive T-cell infusion will be replaced by additional participant(s) assigned to the same dose level.

Additional participants or additional cohorts may be added to perform further evaluation of the efficacy and safety of GSK3901961.

5.3 End of Substudy 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;
- Participant dies;
- Interventional phase ends for the participant's cohort (see Section 5.3.2 of this substudy).

If participant withdraws consent or is withdrawn for other reasons prior to substudy completion, they will be considered early withdrawal. See Core Section 9.2.1 for AE follow-up requirements during the interventional phase.

All participants alive after the Interventional 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, 2020b] 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 occur within 6 months of completing the interventional portion of the study.

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:

- For each cohort in the substudy, the interventional phase ends when 80% of the total number of participants dosed with RP2D in the cohort have confirmed disease progression or died or have been lost to follow-up or withdrawn early, and all the remaining dosed participants in the cohort (including any treated at doses other than the RP2D) have been followed for at least 1 year post infusion or have confirmed disease progression or died or were withdrawn or lost to follow-up from the substudy.
- For the substudy, the interventional phase ends when the interventional phases of all cohorts in the substudy have ended.

b) End of substudy:

- For each cohort in the substudy, the cohort ends when all enrolled participants in the cohort 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.
- The substudy ends when all enrolled participants have moved 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 Justification for Population

The target population for treatment with GSK3901961 of previously treated, advanced (metastatic or unresectable) SS / MRCLS patients; or previously treated metastatic NSCLC patients has taken into consideration the high unmet medical need for both of these settings.

- Inclusion of participants with SS and MRCLS enables GSK to seek early signals of efficacy improvements of GSK3901961 over GSK3377794 (lete-cel), given that data from pilot Studies 208466 and 208469 suggest that GSK3377794 provides clinical benefit in the 2L+ setting.
- By virtue of the enhanced CD8α expression, GSK3901961 may be particularly suitable to deliver enhanced benefit over GSK3377794 in cancers that have lower antigen levels as compared e.g. to SS where NYESO1 is highly and homogenously expressed. Lung cancer may indeed be expressing NYESO1 at a level where transduced T cells may not reach the required activation threshold, which will be supported by the co-expressed CD8α molecule. CD8α expression on the CD4+ TCR transduced T cells will enable these cells, in addition to the CD8+ T cells, to sufficiently bind to the targeted tumor cells and exhibit functional anti-tumor activity, thereby potentiating the cytotoxic activity of the entire T-cell product. Therefore, NSCLC was selected as an additional tumor type for the testing of GSK3901961 in this first-time-in-human substudy

5.5 Justification for Dose

5.5.1 Dosing Rationale

The proposed starting dose range is $1 \times 10^9 - 8 \times 10^9$ transduced T cells, which is also the RP2D for GSK3377794 (lete-cel) and is within the range used in other TCR-T or more generally ACT studies, and also the range that is currently being used for GSK3377794 (lete-cel) clinical trials. If required by the observed DLT rate, the dose range will be lowered to $0.1 \times 10^9 – 0.8 \times 10^9$ transduced T cells.

This proposal to start at RP2D for GSK3377794 (lete-cel) is based on a detailed assessment of the structure and properties of GSK3901961 and its expected mechanism of action, taking into account existing data with GSK3377794 and other ACTs as well as similarities and differences between GSK3377794 and GSK3901961, as described in Section 3.2 of this Substudy and with a few additional points as follows:

- **Clinical data from TCR T-cell products targeting NYESO1 or other ACTs suggest that the proposed dose range should be safe:**
  - GSK3377794 (lete-cel) has been administered at doses as high as 14×10^9 (14 billion) transduced T cells and has demonstrated an AE profile that has generally been manageable and acceptable at all doses administered.
  - In the GSK analysis of clinical data from GSK3377794 (lete-cel), there was no identified dose-vs-toxicity relationship, and an extensive correlative analysis for CRS events did not demonstrate any dose effect.
  - T-cell therapies with the same NYESO1 TCR but using a different viral vector have been found to be well-tolerated at up to 10^{11} (100 billion) cells, without dose limiting toxicity [Robbins, 2015]. To date no DLTs have been reported for any TCR T-cell product targeting NYESO1.

  - Furthermore, the proposed dose is within the range used in other TCR-T or CAR-T studies [Morgan, 2006; Johnson, 2009; Hartmann, 2017; Pettitt, 2018].

- **The TCR has shown no cross-reactivity in nonclinical or clinical studies.**
- **Efficacy has been demonstrated with doses in the proposed target dose range:**
  - In clinical trials higher doses of NYESO1 TCR-engineered T cells were associated with a higher likelihood of clinical responses [Robbins, 2015];
  - In pilot studies with GSK3377794, clinical activity was observed in SS with infusion of 18×10^9 transduced T cells, and peak expansion was correlated with efficacy. The proposed dose range was also associated with higher peak expansion of the infused T cells and T-cell persistence, which appear to correlate with efficacy in internal GSK analyses of GSK3377794 data (results not shown) and similarly for CD19 CAR-T studies [Porter, 2015].

In this substudy, GSK will implement specific safety measures to mitigate risk including split dosing and staggered treatment as described in Study Design, Section 5.1 of this Substudy.

The approach of split-dosing has previously been utilized in initial CAR-T studies in an effort to avert acute severe CRS when the diagnosis and management of these complications was not well defined. Administering a reduced (30%) dose aliquot initially is expected to achieve a more controlled T-cell expansion and limited cytokine release from the infused T cells. The 7-day gap permits immediate action (including possibly delaying, or not administering at all, the second aliquot) in case of early acute toxicities.

Severe acute toxicities associated with ACT typically occur within the first 7 to 15 days. Therefore, initiation of the lymphodepleting regimen in the 2nd and 3rd participant (across both SS / MRCLS and NSCLC) will be separated by a minimum of 2 weeks from the complete dose administered to the prior participant).

5.5.2 Justification of Lymphodepleting Regimen

Based on prior experience with GSK3377794 in participants with synovial sarcoma and melanoma, where a similar lymphodepletion regimen was associated with optimal responses [Mackall, 2016; D'Angelo, 2018], the previously used lymphodepletion regimen was 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 GSK3377794 infusion on Day 1.

Based on additional safety data (prolonged neutropenia; fatal neutropenia [see GSK3377794 IBv13, GlaxoSmithKline Document Number RPS-CLIN-015027, 2021]) and modelling data, to further optimize lymphodepletion 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 regimen is currently in use for NSCLC participants in Study 208471 (slightly different schedule).

The refined lymphodepleting regimen for participants treated as of protocol amendment 02 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 GSK3377794 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 Amendment 01 as follows:

- As of protocol amendment 02, a standard reduction for cyclophosphamide dose (in mg/m^2) of 2700 = 900 × 3 days is to use 1800 = 600 × 3 days

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 and/or LAGE-1a.*
- ***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 GSK3901961.*

6.1 Inclusion Criteria

6.1.1 Target Expression Screening

*Participant is eligible to be screened for target expression (HLA-A*02:01, A*02:05, or A*02:06 and NY-ESO-1 and/or LAGE-1a) only if all of the following criteria apply: [NOTE: criteria indicated as disease-specific only apply to participants with this disease.]*

1. Capable of giving signed informed consent for the Screening process including compliance with the requirements and restrictions listed in the Screening informed consent form and in the protocol.
2. Is ≥18 years of age and weighs ≥40 kg on the day of signing informed consent form.
3. A representative tumor tissue specimen with associated pathology report should be available to perform NY-ESO-1/LAGE-1a (when a designated central laboratory test is available) antigen expression analysis unless the result of a recent test performed under a different GSK-sponsored protocol or substudy and on a platform(s) that

meets the 209012 protocol requirements, is available. For guidance on acceptable specimen material see Tumor Biopsies under Section 5.1.4.

Synovial Sarcoma or MRCLS:

4. Has a diagnosis of SS or MRCLS as confirmed by local histopathology and with evidence of disease-specific translocation. NOTE: Evidence of a disease-specific translocation is required at latest prior to leukapheresis (Inclusion Criterion 12).
5. Has advanced (metastatic or unresectable) SS or MRCLS. Unresectable refers to a tumor lesion in which clear surgical excision margins cannot be obtained without leading to significant functional compromise.

NSCLC:

6. Has histologically or cytologically confirmed Stage IV NSCLC.

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. In addition, the following criteria must also apply:
[NOTE: criteria indicated as disease-specific only apply to participants with this disease.]

7. Is capable of giving signed informed consent for the trial (including the potentially 15-year-long LTFU phase) including compliance with the requirements and restrictions listed in the informed consent form and in the protocol.
8. 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 laboratory prior to leukapheresis.

   NOTE: The result of an HLA test performed under a different GSK-sponsored protocol or substudy, and on a platform(s) that meets the 209012 protocol requirements, is acceptable.

9. Participant's tumor (either the most recent archival specimen or a fresh biopsy) must have tested positive for NY-ESO-1 and/or LAGE-1a expression (when LAGE-1a testing is available) by a GSK designated laboratory (and meets the threshold criteria defined for the specific tumor type).

   NOTE: The result of a recent NY-ESO-1 and/or LAGE-1a expression test (when LAGE-1a testing is available) performed under a different GSK-sponsored protocol or substudy, and on a platform(s) that meets the 209012 protocol requirements, is acceptable in place of the result from a new test performed as part of Target Expression Screening for Substudy 1 (Section 6.3.4).

10. Has measurable disease according to RECIST v1.1.

    NOTE: Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

11. Has evidence of radiographic or clinical disease progression.
12. **SS/MRCLS** 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 Immunohistochemistry (IHC) using fusion-specific antibody are commonly used to detect translocations.
13. Prior therapies for **SS/MRCLS participants**: Participant has completed at least one standard of care treatment including anthracycline containing regimen unless intolerant to or ineligible to receive the therapy. Participants who are not candidates to receive anthracycline should have received ifosfamide unless also intolerant to or ineligible to receive ifosfamide. Participants who received neoadjuvant/adjuvant anthracycline or ifosfamide based therapy and progressed will be eligible.

    NOTE: Participants "intolerant" to a therapy include but are not limited to those who are ineligible to receive therapy due to poor functional status, or have developed Grade ≥3 toxicity necessitating discontinuation, dose modification or unplanned hospitalization to alleviate effects of toxicity [van Abbema, 2019].
14. Prior therapies for **NSCLC participants**:
    a. For NSCLC lacking actionable genetic aberrations (i.e., wild type), per NCCN guidelines: participant has been previously treated with or is intolerant to PD-1/PD-L1 checkpoint blockade therapy and has been previously treated with or is intolerant to a platinum-based chemotherapy. Adjuvant therapy will count as a regimen if completed within 6 months before relapse.

    OR

    b. For NSCLC that harbors actionable genetic aberrations (e.g. BRAF, ALK/ROS1, etc.), per NCCN guidelines: participant has been previously treated with or is intolerant to SOC therapy, including targeted therapy, as recommended by NCCN or equivalent country-level guidelines (e.g., ESMO, NICE).

    OR

    c. Investigator has decided that additional lines of SOC therapy after the first line are not in the participant's best interest. Participant can be considered eligible for the trial only in consultation with the Medical Monitor (or designee).

       NOTE: Participants "intolerant" to a therapy include but are not limited to those who are ineligible to receive therapy due to poor functional status, or have developed Grade ≥3 toxicity necessitating discontinuation, dose

modification or unplanned hospitalization to alleviate effects of toxicity [van Abbema, 2019].

15. Performance status: Eastern Cooperative Oncology Group (ECOG) of 0-1.
16. Predicted life expectancy that is ≥6 months.
17. Left ventricular ejection fraction ≥45% with no evidence of clinically significant pericardial effusion or as per institution's guidelines.
18. In the Investigator's opinion, the participant is fit for leukapheresis and has adequate venous access for the cell collection.
19. Participant must have adequate organ function and blood cell counts within 7 days prior to the day of leukapheresis (and prior to first day of lymphodepletion during Treatment fitness assessment), as indicated by the laboratory values in Table 9.

Table 9 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)	≥0.5x 10^9/L
Hemoglobin	≥8 g/dL or ≥5.0 mmol/L (not achieved by transfusion) [a]
Platelets	≥100 x10^9/L (not achieved by transfusion) [b]
Renal	
Creatinine clearance ≥50 mL/min for NSCLC and ≥40 mL/min for SS/MRCLS: • Participants who are ≥18 and <65 years of age must be assessed either: a. by 24-hour urine creatinine collection OR b. 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 Section 7.1.3 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.	

System	Laboratory Value
Hepatic	
Albumin	≥3.5 g/dL
Total bilirubin Participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)	≤1.5 × ULN (isolated bilirubin ≤1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
ALT	≤2.5 × ULN (or ≤5 × 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

a. No red blood cell transfusions to meet minimum hematologic values for eligibility.
b. No platelet transfusions within 14 days.
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 waived to proceed with lymphodepletion.
d. Prior to **lymphodepletion**, please refer to Substudy 1 Section 7.5.2 for guideline on use of anticoagulant medication.

20. 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 starting at the first dose of chemotherapy during lymphodepletion 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.

    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 of the Core protocol

  OR

- Is a WOCBP (as defined in Core 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 Core Section 12.4 for appropriate periods prior to leukapheresis and prior to the first dose of chemotherapy during lymphodepletion and continuing until 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.

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.

21. Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test
    - 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.
    - 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.

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:
[NOTE: criteria indicated as disease-specific only apply to participants with this disease.]

22. Has documented radiographic evidence of disease progression from prior line of therapy.

    NOTE: Lesions situated in a previously irradiated area are considered measurable per RECIST v.1.1 if progression has been demonstrated in such lesions.

23. A biopsy of non-target tumor tissue (e.g., excisional, incisional, or core) obtained within 28 days prior to initiating lymphodepleting chemotherapy is mandatory if clinically feasible. This biopsy will be used as baseline for CCI analyses. If there is only 1 measurable lesion and non-target lesions are absent or not accessible,

Medical Monitor (or designee) must be consulted and biopsy may be performed if there is no anticipated risk of interfering with measurement of single lesion. If it is not feasible to obtain a fresh biopsy, other options including 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 anti-cancer therapy, the screening biopsy will be used for baseline.

24. 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 and/or LAGE-1a) if any of the following criteria apply:*
[NOTE: criteria indicated as disease-specific only apply to participants with this disease.]

1. 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 (melanoma in situ, basal cell carcinoma, prostate ca 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
2. 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

3. Previous treatment with genetically engineered NYESO1-specific T cells, NYESO1 vaccine, or NYESO1 targeting antibody.

   Exception: Participants who achieved a confirmed RECIST v1.1 response of CR or PR or SD ≥3 months following treatment with letetresgene autoleucel (GSK3377794, lete-cel) on another GSK sponsored study/substudy may be considered for eligibility to this substudy following discussion with the Sponsor Medical Monitor.

4. Prior gene therapy using an integrating vector.

   Exception: Participants who achieved a confirmed RECIST v1.1 response of CR or PR or SD ≥3 months following treatment with letetresgene autoleucel (GSK3377794, lete-cel) on another GSK sponsored study/substudy may be considered for eligibility to this substudy following discussion with the Sponsor Medical Monitor.

5. Previous allogeneic hematopoietic stem cell transplant within the last 5 years or solid organ transplant.

6.2.2 Leukapheresis Eligibility Screening

Participants are not eligible for leukapheresis 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 10) before starting leukapheresis. In addition, participants are not eligible for leukapheresis if any of the following criteria apply: [NOTE: criteria indicated as disease-specific only apply to participants with this disease.]

6. Participant has central nervous system (CNS) metastases.

   - **Exception: NSCLC participants** with treated asymptomatic CNS metastases (supratentorial or cerebellar) may be eligible after discussion and agreement with the Sponsor Medical Monitor (or designee), and they meet all of the following criteria:

     a. Clinically stable

     b. No history of bleeding within CNS metastases

     c. No lesions in the brain stem, midbrain, pons, medulla or spinal cord

     d. No leptomeningeal metastases

     e. No spinal cord compression

     f. Not requiring escalating anti-epileptic treatment

     g. Not requiring ongoing treatment with steroids for CNS disease

     h. Adhere to a 2-week washout period for focal radiotherapy (e.g., gamma knife radiosurgery)

     i. Adhere to a 4-week washout period for whole brain radiotherapy

     j. Adhere to a 3-month washout period for therapy to any CNS metastases if they are to be considered as target lesions

k. A repeat brain MRI prior to lymphodepletion would need to show stability or reduction of CNS metastases.

- **Exception: <u>NSCLC participants</u>** who develop oligometastatic CNS metastasis (supratentorial or cerebellar) after leukapheresis and prior to start of lymphodepletion may be eligible to continue with lymphodepletion after discussion and agreement with the Sponsor Medical Monitor (or designee), and they meet all of the following criteria:
  a. Asymptomatic
  b. Small volume of disease (defined as no more than 3 lesions, each ≤0.5 cm)
  c. Not requiring steroids or anti-epileptic treatment
  d. Treatment of the lesions is not clinically indicated.

7. Participant has a 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.
8. 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.
9. Uncontrolled intercurrent illness including, but not limited to the following:
   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. Severe aortic stenosis, symptomatic mitral stenosis
   f. Interstitial lung disease (participants with existing pneumonitis as a result of radiation are not excluded; however, participants cannot be oxygen dependent)
10. Insufficient pulmonary function with mechanical parameters <40% predicted (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], total lung capacity [TLC], pulmonary diffusing capacity for carbon monoxide [DLCO])
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, esophageal, 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 according to the site practices, machine-read or manually over-read.

Only one preferred formula should be used to calculate the QTc for an individual participant; multiple formulae should not be used.

For purposes of data analysis, either QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the SAP.

13. Participant has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.
14. Participant has active infection with HIV, HBV, HCV, EBV, CMV, syphilis, or HTLV as defined below:
    - Positive serology for human immunodeficiency virus (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 Epstein-Barr virus (EBV) infection. Participants with positive EBV serology will undergo additional tests/assessments in order to rule out active infection;
    - Active cytomegalovirus virus (CMV) infection. Participants with positive CMV serology will undergo additional tests/assessments in order to rule out active infection;
    - Positive test for syphilis (spirochete bacterium);
    - Positive serology for human T lymphotropic virus 1 or 2 (HTLV-1 or 02).
15. Pregnant or breastfeeding females (due to risk to fetus or newborn).
16. 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. Bridging or intermediate standard of care anti-cancer treatment is allowed but washout periods in Table 10 should be followed.
17. Investigational treatment within 4 weeks or 5 half-lives (whichever is shorter) prior to leukapheresis. Investigational vaccines (other than NYESO1 vaccines that are not allowed) must follow the washout period specified in Washout Period Table 10

below. Exceptions to this rule must be evaluated by the Investigator in agreement with the Sponsor's Medical Monitor (or designee).

NOTE: Investigational treatment is not allowed between leukapheresis and study intervention.

6.2.3 Treatment Eligibility Screening

Please note that mandatory washout period restrictions must be respected (Table 10) before starting lymphodepletion. In addition to confirming treatment fitness per Section 6.2.3.1 , participants are not eligible for lymphodepletion or treatment if any of the following criteria apply:
[NOTE: criteria indicated as disease-specific only apply to participants with this disease.]

18. Participant has received cytotoxic therapy within 3 weeks prior to lymphodepleting chemotherapy.
19. Participant has received 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 lesion(s) 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.
22. Radiotherapy that involves the lung (V20 exceeding 30% lung volume or mean heart dose >20Gy) within 3 months OR radiotherapy (including but not limited to palliative radiotherapy) to lung/mediastinum with V20 less than 30% lung volume and with mean heart dose ≤20Gy within 4 weeks (±3 days):

    NOTE:

    a. Electron beam radiotherapy to superficial structures in the chest is permitted.
    b. There is no wash-out period for palliative radiation to non-target lesions other than the lung and mediastinum.
23. Participant has received an anti-cancer vaccine within 2 months of lymphodepletion in the absence of tumor response. The participant should be excluded if their disease is responding to an experimental vaccine given within 6 months of lymphodepletion.
24. Participant has received live vaccine within 4 weeks prior to lymphodepletion.
25. Participant has received immune therapy (monoclonal antibody therapy, checkpoint inhibitors) within 4 weeks of lymphodepletion.
26. Participant had major surgery within 4 weeks prior to lymphodepletion.

Table 10 Washout Periods

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 or 5 half-lives (whichever is shorter)	Not allowed
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 with the exception of non-target lesions in the lung and mediastinum for which the washout period prior to lymphodepletion is 4 weeks.
	For **NSCLC participant** with treated asymptomatic CNS metastases: • 2-week washout period for focal radiotherapy • 4-week washout period for whole brain radiotherapy	
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 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, and any serious adverse events (SAEs).

6.3.4 Screening Under Other GSK Studies

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

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

6.3.5 Rescreening/Transfer

Individuals who do not meet the criteria for participation in this study or another GSK-sponsored similar study or substudy of this protocol (screen failure for reasons other than NYESO1 or HLA status) may be rescreened or transferred.

For each rescreened/transferred 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 laboratory 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 GSK designated laboratory under this substudy or under

another GSK-sponsored study or substudy of this protocol, with confirmed positive NY-ESO-1/LAGE-1a expression for the indication;

- 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 GSK3901961 if within shelf-life specifications;
  - Already stored manufactured GSK3901961 product under an applicable process may be used for the T-cell infusion if within shelf-life specifications.

6.3.6 Potential Eligibility of Participants Who Have Previously Received Letetresgene Autoleucel (Lete-Cel)

Participants who achieved a confirmed RECIST v1.1 response of CR or PR or SD ≥3 months following treatment with letetresgene autoleucel (GSK3377794, lete-cel) on another GSK sponsored study may be considered for eligibility to this substudy (see Section 6.3.7.1).

6.3.7 Conditions for Inclusion of Participants Who Have Previously Received Letetresgene Autoleucel (Lete-Cel)

Consideration for eligibility on a case by case basis will include the following conditions, in addition to meeting eligibility criteria in the relevant substudy (Section 6.1 and Section 6.2):

- Participant had a confirmed CR or PR or SD ≥3 months following treatment with letetresgene autoleucel on a GSK sponsored study;
- Participant's disease subsequently progressed no earlier than 12 weeks after infusion of letetresgene autoleucel;
- Participant has not received systemic anti-cancer therapy for the treatment of their disease with the exception of bridging therapy which is permitted;
- Eligibility based on NY-ESO-1/LAGE-1a target expression from fresh biopsy is confirmed (from 1st infusion progression biopsy optimally obtained prior to receipt of any additional systemic anti-cancer therapy). If acquisition of a post-progression biopsy sample is not feasible, alternatives may be discussed with the Medical Monitor or designee;
- Participant meets the substudy eligibility criteria with the exception of
  - Exclusion criterion #3: "Previous treatment with genetically engineered NY-ESO-1-specific T cells, NY-ESO-1 vaccine, or NY-ESO-1 targeting antibody"
  - Exclusion criterion #4: "Prior gene therapy using an integrating vector"
- Participant did not experience a Grade 4 CRS event or Grade 4 neurologic toxicity after the first NYESO1 specific T-cell infusion;

- Toxicities related to conditioning chemotherapy and infusion of letetresgene autoleucel, with the exception of alopecia, have resolved to Grade ≤1 or returned to baseline prior to initiation of lymphodepletion for treatment with next generation NYESO1 specific T cells.

Consideration of such participant for eligibility assessment to this trial must first be agreed with Sponsor taking into account benefit-risk for the specific patient.

No such participants will be permitted on this substudy until at least the dose confirmation phase is complete.

No more than 3 participants who were previously treated with letetresgene autoleucel will be permitted in this substudy.

6.3.7.1 Benefit:Risk Assessment for Inclusion of Participants Who Have Previously Received Letetresgene Autoleucel (Lete-Cel)

Prior clinical experience of retreatment with the same T-cell product across multiple studies of CAR and TCRs, including GSK3377794 (lete-cel), supports the consideration of enrolling participants who have previously received GSK3377794 into this substudy with GSK3901961 which, target the same NYESO1 epitope as GSK3377794. In two studies conducted at the pediatric [Lee, 2015] and Surgery Branch [Kochenderfer, 2015] of the National Cancer Institute (NCI) 6 subjects were re-treated upon progression. Three of the re-treated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression. Gauthier et al, [Gauthier, 2021] demonstrated that second infusions of CAR-T therapy were both feasible and induced responses in 39% of subjects, including CRs in 20%. Evidence of tumor regression post disease progression following a second infusion of TILs was demonstrated by Tran el al, [Tran, 2014] in a subject with cholangiocarcinoma. Similarly Hegde et al [Hegde, 2020] reported a second remission (CR) in a child with rhabdomyosarcoma following retreatment with HER2 CAR T cells following progression 6 months post first CAR T infusion.

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

In Study 208466, many of the subjects who underwent initial treatment with GSK3377794 (lete-cel) demonstrated clinical benefit, with measurable tumor regression by RECIST 1.1 and investigator assessment observed in one third (33%) of subjects. On retreatment (11 participants), 1 CR, 1 PR, and multiple SD were observed. In Study 208749, 1 subject received a second infusion post progression and achieved SD.

Ultimately, the benefit:risk has been maintained in participants who received GSK3377794 (lete-cel) for a second time.

Enrolment of participants who have received GSK3377794 (lete-cel) will only be permitted once the dose confirmation phase is complete, when early safety and efficacy data on GSK3901961 is available. A limited number of participants will be permitted and only following agreement between Sponsor and Investigator. Participants will be assessed on a case-by-case basis, including evidence of acceptable safety and evidence of efficacy demonstrated by a confirmed CR or PR or SD ≥3 months following initial infusion of GSK3377794 (see Section 6.3.7 for details).

The risk of receiving GSK3901961 after GSK3377794 (lete-cel) is considered similar to that of treating a participant with GSK3901961 for the first time. On this basis, in the context of patients with limited alternative treatment options, the benefit:risk for enrolling participants who have received GSK3377794 is considered acceptable.

7 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s) described below intended to be administered to a study participant according to the study protocol.

7.1 Study Intervention(s) Administered

7.1.1 Leukapheresis

Participants will undergo leukapheresis to obtain starting material for the manufacture of GSK3901961.

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

A CD3 count of at least 200/μL prior to leukapheresis is recommended to ensure an adequate T-cell collection for manufacture of GSK3901961. If the laboratory 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 laboratory test should be repeated, and the Sponsor alerted as soon as possible. Should there be any manufacturing issues, such as failure, additional collection(s) may be required.

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

Since HLA-typing and NY-ESO-1/LAGE-1a expression testing are required prior to treatment, bridging or 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 10) must be respected when planning treatment or procedure.

Additionally, systemic chemotherapy may be administered between Leukapheresis and the start of Lymphodepletion, if a participant has progressive disease and cannot be treatment-free. Mandatory washout periods prior to lymphodepletion (see Section 6.2 Table 10) must be respected when planning treatment or procedure.

At the discretion of the Investigator and after discussion with the Medical Monitor, bridging therapy may be considered for any participant, particularly those with high disease burden or disease-related symptoms at screening.

Administration will be based on Investigator's evaluation of risk/benefits, 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 in the Core Protocol and the SOA in this Substudy. Disease progression after prior line of treatment needs to be documented prior to performing lymphodepletion.

When the GSK3901961 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 11. Cyclophosphamide and fludarabine will be supplied by the pharmacy of the participating Institution. **Chemotherapy for all tumor types will be administered on Days -7 to -4. The doses administered and the schedule of administration are presented in Table 11**.

Dose and regimen for lymphodepleting chemotherapy is adjusted for participants ≥60 years of age, as specified in Table 11. 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).

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 9 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 GSK3901961 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 Core Section 12.7.

Table 11 Lymphodepleting Chemotherapy for Participants

	Lymphodepleting chemotherapy					**Recommended prophylaxis and supportive medication**
Day	**Drug**	**Dose, mg/m²**	**Dose for participants ≥60 years old, mg/m²**	**Route**	**Administration**	Infection: On admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Core 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 h after the last cyclophosphamide infusion. 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 h [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 h [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 h [2]	
-3	start G-CSF[4]					
-2, -1	There is no day 0 on this study					
+1	GSK3901961					

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 and weight-related modifications. 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 as described in this section. This adjustment needs to be applied to all doses, on top of the age-related and renal impairment 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; h = hour(s); 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 modifications. 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 9 for calculation steps before comparing to the thresholds given above.

If estimating CrCl renal function 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 and tumor-related modifications. If the participant's weight is greater than 175% Ideal Body Weight (IBW), then calculate cyclophosphamide dose based on Body Surface Area (BSA) calculated using the 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 Adjusted 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.

Mesna

Mesna should be administered per institutional guidelines or as recommended below: 50% of cyclophosphamide daily dose (450 mg/m^2 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 GSK3901961 Infusion

Refer to the current version of the IB regarding GSK3901961 and related clinical experience. Refer to the Drug Product and Infusion Manual for details and instructions on storage and administration of GSK3901961.

Participants will receive GSK3901961 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 Core 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.

GSK3901961 Dose

The intended dose of GSK3901961 will be within the range of $1 \times 10^9 – 8 \times 10^9$ transduced T cells, which will be administered by a single intravenous infusion on Day 1 unless the participant is a sentinel participant who will receive split dosing (see Section 5.1.1 of this Substudy). The minimum transduced cell dose for meeting release criteria is 1×10^9.

In the event dose de-escalation is required, the dose range will be lowered 10-fold to $0.1 \times 10^9 – 0.8 \times 10^9$ transduced T cells. The minimum transduced cell dose for meeting release criteria in case of dose de-escalation is 0.1×10^9.

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.

Additional Dosing Considerations

See Study Design Section 5.1 in this Substudy for split dosing and staggered dosing in the sentinel participants.

GSK3901961 Administration

Participants will be admitted into the hospital on the day of T-cell infusion and will be hospitalized for follow-up care post T-cell infusion for at least 3 days after receiving T-cell infusion and at the discretion of the Investigator thereafter. Participants will maintain close follow up with the Investigator for 2 weeks following T-cell infusion.

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.

Dosing and follow-up for sentinel participant(s) is described in Section 5.1.1 of this Substudy.

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 or stopped, and the reaction managed according to institutional standard procedures (Core 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 Core 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 IP 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 preparation, handling, storage, accountability and 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 IP. 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 study.

7.4 Study Intervention Compliance

GSK3901961 will be intravenously administered to participants at the site per guidelines specified in the Drug Product and Infusion Manual. Other study interventions will be administered as described in this protocol and per institutional guidelines.

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 from the timepoints specified in the washout Table 10 before the start of study intervention and 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 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 Core 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 [Smith, 2015], steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of the IP. Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

Systemic glucocorticoids are prohibited for any purpose other than to treat an event of suspected immunologic etiology (see Core 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. 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 designated 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 CCI 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 10 of this Substudy.

Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

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 Medications and Supportive Care

Anti-IL-6 drugs such as Tocilizumab may be administered to participants experiencing cytokine release syndrome (Core 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 Core Section 12.7 for details on general supportive care that can be given during the study.

7.6 Dose Modification

See Section 5.1 of this Substudy for split dosing and staggered treatment for the sentinel participants. Once dose confirmation phase is complete, 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 or as otherwise instructed. 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 by the sponsor after the end of the study. Participants 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.

In this substudy, Liver chemistry and QTc stopping criteria described in Core Protocol Section 8 will apply only to the participants who receive study intervention dose as a split infusion (sentinel participants).

9 STUDY ASSESSMENTS AND PROCEDURES

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

There are no substudy-specific assessments in this Substudy. Dose selection committee will be engaged in this study.

9.1 Dose Selection Committee

In this Substudy, the DSC will be established for making dose recommendations based on a review of all relevant data. The DSC will include participating investigators as well as GSK representatives from functional groups including safety, clinical, statistics and may also include external experts that are not involved in the study. The committee will be tasked to determine whether the same dose can be given to additional participants; or decide to move to a lower dose level or to a higher dose level as guided by the mTPI-2 model (described in Section 5.1.1 of this Substudy). In absence of DLTs, DSC will meet after every 3 participants have received the dose and been followed for a minimum of 4 weeks. Ad hoc DSC meetings may also be held at other time points if deemed necessary (i.e. for DLT discussion). DSC will be in place until the end of Dose Confirmation Phase. Additional details on the DSC will be provided in the Dose Selection Plan.

10 STATISTICAL CONSIDERATIONS

The following substudy-specific considerations are in addition to those specified in the Core Protocol Section 10.

10.1 Statistical Hypotheses

The primary objectives of this study are safety, tolerability and determining the RP2D of GSK3901961. All analyses will be descriptive.

10.1.1 Modified Toxicity Probability Interval 2 (mTPI-2) Based Dose Confirmation Design

The dose confirmation phase of this study is based on an mTPI-2 [Guo, 2017] design. mTPI-2 is implemented within a formal Bayesian decision framework and is extension of

the modified toxicity probability interval method (mTPI) [Ji, 2010]. mTPI-2 was chosen over mTPI because it is more preventative against overdosing and non-intuitive decision making, resulting in an improved decision table that uses the same estimation procedure for the maximum tolerated dose as mTPI. Additionally, mTPI-2 preserves the simple and transparent nature of mTPI with Bayesian statistical modifications.

The choice of this design is validated by simulation results found in Core Section 12.10: mTPI-2 Design Simulation Results.

The three dosing intervals are associated with three different dose-escalation decisions. The under-dosing interval corresponds to a dose re-escalation (R), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S), found in Table 8 of Section 5.1.1.2 of this Substudy. Similar to mTPI, mTPI-2 employs a simple beta-binomial hierarchic model. Decision rules are based on calculating the unit probability mass (UPM) of three classifications of intervals corresponding to under dosing, proper dosing, and overdosing in terms of toxicity. It is assumed that the target toxicity is defined as pT. The unit interval (0,1) is divided into equal length subintervals of size (e1+e2), such that the proper dosing interval is (pT – e1, pT + e2), the under-dosing intervals are all intervals contained in (0, pT – e1), and the overdosing intervals are all intervals contained in (pT + e2, 1), where e1 and e2 are small fractions to account for the uncertainty around the true target toxicity. If the proper dosing interval has the highest UPM, it is chosen as the winning model and the dosing decision is to stay at the current dose. If any interval contained in the under-dosing interval has the highest UPM, it will be chosen as the winning model and the decision is to escalate the next cohort to a higher dose. If any interval contained in the over-dosing interval has the highest UPM, it will be chosen as the winning model and the decision is to deescalate the next cohort to a lower dose. Guo et al. [Guo, 2017] shows that the decision based on the UPM is optimal in that it minimizes a subsequent expected loss. Under the mTPI-2 design, a dose confirmation phase is terminated when either the lowest dose is above the MTD or a prespecified maximum sample size is reached. The phase will be completed if ≥6 subjects are treated, and the observed toxicity is ≤1/3. For this study, pT, the target toxicity level, is 0.3 and the uncertainty values are set at e1=e2=0.05.

10.2 Sample Size Determination

10.2.1 Sample Size for Cohort 1

Once the RP2D has been established, the substudy cohorts will expand to up to n=10 participants each treated at that dose.

The hypothesis for cohort 1 (NSCLC) is H_0: 10% v. H_1: 30%. This cohort size was chosen to allow for early stopping of further development due to futility if the posterior probability that the ORR is less than 30% is >96%. This is equivalent to observing 1 or fewer responders out of 10 treated participants. An uninformative Beta (a=0.01, b=0.09) prior was used. Additionally, if the true ORR is 10%, the probability of observing 1 or fewer responder out of 10 treated participants is 74% and if the true ORR is 30% the probability of observing 1 or fewer responder out of 10 treated participants is 15%.

10.2.2 Sample Size for Cohort 2

The hypothesis for Cohort 2 (SS / MRCLS) is H_0: 40% v. H_1: 60%. This cohort size was chosen to allow for early stopping of further development due to futility if the posterior probability that the ORR is less than 60% is >90%. This is equivalent to observing 4 or fewer responders out of 10 treated participants. An uninformative Beta (a=0.02, b=0.08) prior was used. Additionally, if the true ORR is 40%, the probability of observing 4 or fewer responders out of 10 treated participants is 63% and if the true ORR is 60% the probability of observing 4 or fewer responders out of 10 treated participants is 17%.

These decision rules are for guidance only and the final decision for stop for futility will be determined on totality of data.

If supported by safety and efficacy results, additional participants may be enrolled to confirm the safety and efficacy via a protocol amendment or as part of a separate protocol. For cohort 1, two or more confirmed responses (CR or PR) out of 10 evaluable participants treated at RP2D may provide sufficient efficacy evidence to enroll additional participants. For cohort 2, five or more confirmed responses (CR or PR) out of 10 evaluable participants treated at RP2D may provide sufficient efficacy evidence to expand and enroll additional participants. This will serve as guidance for final decisions regarding enrollment of additional participants, which will be based on a review of the totality of the data. Additional details will be provided in the SAP.

10.3 Data Analysis Considerations

In the dose confirmation phase, the dose will be re-escalated/de-escalated based on all available data, including safety laboratory data, CCI and PK data and the safety profile observed. The DLT information on all participants enrolled in the trial is used to update the estimated dose toxicity relationship and provide supportive information in addition to the mTPI-2 design in the next re-escalation/de-escalation decision; the mTPI-2 approach is expected to be used as the primary criteria for dose escalation.

10.4 Populations for Analyses

Additional analysis populations to those specified in the Core Protocol Section 10.4 may be defined in the SAP.

10.5 Statistical Analyses for Cohort 1 and 2

10.5.1 Interim Analysis

An interim analysis will be performed for each cohort after 10 participants in the cohort are evaluable at the RP2D. These analyses may be performed earlier with fewer than 10 evaluable participants at the RP2D if it is clear from the accumulated data what the decision at 10 evaluable participants treated at RP2D would be. For example, if in Cohort 1 (NSCLC) no responders are observed in the first 9 evaluable participants at the RP2D, or if in cohort 2 (SS / MRCLS) no responders are observed in the first 6 evaluable participants at the RP2D then an early interim analysis for that cohort may be conducted.

Details will be specified in the SAP. In the event that an early futility decision is made then enrollment to the cohort will be closed.

10.5.2 Key Elements of Analysis Plan

10.5.2.1 Primary Analysis

The primary analysis for each cohort will be performed after enrollment to the cohort is complete and all the enrolled participants in the cohort that will receive T-cell infusion have done so and of those: at least 80% of those dosed at the RP2D have confirmed disease progression or died or were withdrawn or lost to follow-up from the substudy; and all the remaining infused participants (including any treated at doses other than the RP2D) have completed at least 2 post baseline disease assessments since infusion or have confirmed disease progression or died or were withdrawn or lost to follow-up from the substudy.

If the primary analysis for a cohort is expected to occur within 9 months of the final analyses for the cohort, then the primary analysis may be omitted and only the final analyses carried out. For example if all infused participants in a cohort alive at the end of their interventional phase will promptly transfer to the separate LTFU protocol, then the primary analysis for the cohort may be omitted since the final analysis for the cohort will occur shortly after the end of the interventional phase which (from the definition in Section 5.3.2 of this substudy) will be at most 9 months after the criteria for the primary analysis are first met.

10.5.2.2 Final Analysis

The final analysis for each cohort will be performed after enrollment to the cohort is complete and all the enrolled participants in the cohort that will receive T-cell infusion have done so and of those: all have completed the substudy (as defined in Section 5.3.1 of this substudy) or were withdrawn or lost to follow-up from the substudy.

Complete details of the analyses will be found in the SAP.

10.5.2.3 Safety Analyses

Additional safety analyses to those described in the Core Protocol Section 10.5.2.1 may be specified in the SAP.

10.5.2.4 Efficacy Analyses

Additional efficacy analyses to those described in the Core Section 10.5.2.2 may be specified in the SAP.

10.5.2.5 PK, PD, and CCI [redacted] Analyses

PK (T-cell expansion/persistence), pharmacodynamic (PD), and CCI [redacted] analyses will be described in more detail in the SAP and other supporting documents.

CCI

[redacted]

Pharmacokinetic Analysis

T-cell vector copies (expansion/persistence) in the peripheral blood will be measured in participants by quantitation of transduced cells by PCR of transgene from DNA extracted from PBMC. Persistence will be measured to establish the relationships with response to GSK3901961 as well as a long-term safety measure. For all PK analyses, expansion/persistence of the engineered T cells will be applied in lieu of "concentration" to derive PK parameters. Pharmacokinetic parameters will be calculated by standard noncompartmental analysis according to current working practices and using appropriate software. All calculations of non-compartmental parameters will be based on actual sampling times. PK data from this study may be combined with PK data from other studies and analyzed using population PK approaches, with descriptive statistics presented by treatment, dose and population.

If performed, the population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

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12 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.

12.1 Amendment 1 (21 May 2021)

Overall Rationale for Amendment 01:

The primary rationale for protocol Amendment 01 is .

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

Section # and Name	Description of Change	Brief Rationale
Substudy 1		
2. Schedule of activities Table 1. Substudy 1 Schedule of Activities – Screening and Leukapheresis	Footnote #1 (Table 1) has been amended to state that consent for Leukapheresis and Treatment must be repeated if given more than 90 days prior to leukapheresis procedure. Minor wording clarifications for footnotes #3, 5 and 8. Footnote #4 clarifies that optional Genetics sample "may be collected any time from signature of optional consent until leukapheresis". Footnote #9 clarifies that "CD3 count prior to leukapheresis should preferably be performed with 24 hours prior to leukapheresis procedure". Footnote #10 aligns with Core Protocol Section 9.1.5 on Vital Signs collection, allowing institutional standard methods for collection. Footnote #17 added to reference details of renal assessment in Substudy 1 Section 6.1 Table 9.	Clarification and alignment of SOA with other section changes
2. Schedule of activities Table 2. Substudy 1 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment and Follow-up) And Table 4. Substudy 1 Schedule of Activities – Interventional Phase (Lymphodepletion, Treatment and Follow-up) for Split Dosing	Added standard method of conversion for calendar visit scheduling between month to week, and week to day. Combined Transgene Copies (Persistence for Safety) and CCI [redacted] rows into one as only one sample will be collected to perform both tests. Footnote #16 clarified to instruct that "CT/MRI assessments only need to continue until confirmed PD". Added requirement for ferritin, troponin and NT-proBNP / BNP test prior to Lymphodepletion (Table 2) Added Coagulation assessments for baseline, Day 1 thru 4, Day 6, Day 8, and Day 15 (Table 2) Included requirement for suspected CRS or ICANS to monitor chemistry, hematology, ferritin, coagulation and C reactive protein labs, daily for a week then every other day until symptoms are improving or an alternative diagnosis is confirmed. Included requirement for monitoring of troponin and NT-proBNP / BNP labs for CRS grade≥2 as clinically indicated.	Clarification and alignment of SOA with other section changes Addition of CCI [redacted] and coagulation tests. Clarification of schedule of assessment for suspected CRS or ICANS.

Section # and Name	Description of Change	Brief Rationale
	Minor clarifications to footnote #33 to extend window of collection of genetic sample until first day of lymphodepletion and footnote #34 to clearly identify start of lymphodepletion day per indication.	Clarification of SOA footnotes.
2. Schedule of activities Table 3. Substudy 1 Schedule of Activities – PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) And Table 5. Substudy 1 Schedule of Activities – PK, Immunogenicity, and CCI - Interventional Phase (Treatment and Follow-up) for Split Dosing	Clarified that Sample Type for dnTGF-βRII should be "whole blood" instead of PBMC. Removal of Day 64 since Week 10 visit is not showing on the table (per footnote #1). Updated Requirement for on-study biopsy at Week 4 instead of Week 6 (Footnote #9 specifies that the window of collection for the Week 4 biopsy is extended from Day 21 to Day 39). Corrected schedule of collection for Cytokine Analyses (removal of Week 5, 7 and 9 collections) Updated footnote #5 related to collection of cytokines when CRS is suspected, to reference local laboratory monitoring	Clarification and alignment of SOA with other section changes
2. Schedule of activities Table 6. Substudy 1 Schedule of Activities – Follow-up after Disease Progression or after Completion of Interventional Phase Follow-up	Combined Transgene Copies (Persistence for Safety) and CCI rows into one as only one sample will be collected to perform both tests. Clarified language to align with Long-term Follow-up Study 208750, including: - Discontinuation of persistence/CCI at ≥2 year post T-cell infusion for participants whose transduced T cells are undetected for 2 consecutive visit assessments - Allow medical evaluations to take place via telemedicine (e.g. phone call or video conferences) and/or home healthcare where country and/or local regulations allow - Added option of remote visits for years 6-15	Clarification and alignment of SOA with other section changes
3.2.1 Risk Assessment Table 7. Risk Mitigation Strategy	Corrected reference to IP as GSK3901961 for Substudy 1. Updated risk assessment table: - To include risks of decreased vision and peripheral neuropathy for lymphodepleting chemotherapy (fludarabine/cyclophosphamide); - To include/amend risks of haematopoietic cytopenias, hypersensitivity, reactivation of previous viral infections after prolonged	Update to risk mitigation.

Section # and Name	Description of Change	Brief Rationale
	leukopenia, neutropenia (including fatal neutropenia) decreased vision, to TCR-T infusion - To remove risk of pulmonary toxicity as it should only be specific to substudy 2.	
4. Objectives and Endpoints	Reformatted Secondary Objectives and Endpoints into "Secondary – Efficacy" and "Secondary – Pharmacokinetics". Recategorized [redacted]" as Exploratory objective instead of secondary objective. Combined Frequency and severity of Adverse Events (AEs), Serious AEs (SAEs) and AEs of Special Interest (AESIs) as one single endpoint. Optimized description of Secondary – Pharmacokinetics objectives and endpoints. Updated list of abbreviations.	To clarify subcategories of secondary objectives. Update to [redacted] plan. Standardization of reporting. Clarification of Pharmacokinetics plan. Finalization of table.
5.1.1. Dose Confirmation Phase And 6.1 Former Inclusion #10 (deleted) And 6.1 Former Inclusion #16 (now Inclusion #13) And 6.2 Former Exclusion #1 (deleted)	Cohort 1 metastatic NSCLC participants must have received prior to lymphodepletion (Inclusion #13) a PD-1/PD-L1 checkpoint blockade therapy "and, in the same or different line of treatment, a platinum containing chemotherapy, or participant is intolerant to it". Cohort 1 metastatic NSCLC participants arborring an actionable genetic aberration (e.g., BRAF, ALK/ROS1) per NCCN guidelines, must also have received prior to lymphodepletion (Inclusion #13) "the standard of care (SOC) targeted therapy as recommended by NCCN or equivalent country-level guidelines (e.g., ESMO, NICE)".	Clarification on disease characteristics for inclusion of Cohort 1 NSCLC participants. Removal of any requirement of specific anti-cancer treatment prior to leukapheresis.
5.1.1.1 Determining the R2PD	Minor clarification to the RP2D suggested dose which will have ≥6 participants treated at this dose and an observed toxicity rate ≤1/3.	Clarification of threshold for suggested RP2D dose.
5.1.3 Participant Journey	Optimization of wording to Participant journey description to align with equivalent Core Protocol Section 5.2.	Alignment of wording with equivalent Core protocol section
5.1.4 Tumor Biopsies (new section added) And	Added requirements for on-study tumor biopsies	Clarification.

Section # and Name	Description of Change	Brief Rationale
6.1 Former Inclusion Criterion #5 (now Inclusion Criterion #3) 6.1 Inclusion Criterion #24	A representative tumor tissue specimen [archived or fresh biopsy] with associated pathology report should be available to perform NY ESO 1 antigen expression analysis unless an appropriate recent NY-ESO-1 expression result is already available. Clarification of requirements for baseline biopsy.	
5.3 End of Substudy definition	Clarification of end of Interventional Phase and end of substudy for individual participants as well as for the entire substudy/cohort	Clarification of patient disposition
5.1 Overall Design 6.1 Inclusion Criteria 6.2 Exclusion Criteria	Optimization of Treatment Fitness and Eligibility criteria prior to Lymphodepletion	Removed requirement for repetition of all assessments for eligibility criteria that were already met prior to leukapheresis. Replaced by a Treatment Fitness assessment of the safety criteria in consultation with Medical Monitor.
6.1 Former Inclusion #6 moved to Inclusion #4	Clarification on translocation requirement for inclusion of SS participants (Cohort 2): Methods, such as, but not limited to, Fluorescence in situ hybridization (FISH) assay or Next Generation Sequencing (NGS) are commonly used to detect translocations.	Facilitate inclusion of SS participants on the basis of confirmed histology only.
6.1 Former Inclusion #3 moved to Inclusion #10 And Former Inclusion #4 moved to Inclusion #11 And 6.1 Former Inclusion #14 (now Inclusion #23)	Participants must have measurable disease by RECIST v1.1 (Inclusion #10) and evidence of radiographic or clinical disease progression only prior to leukapheresis (Inclusion #11). Participants must have documented radiographic evidence of disease progression from prior line of therapy prior to lymphodepletion (Inclusion #23).	Clarification on disease requirements to allow for participants who have not progressed to undergo Target Expression Screening.
6.1 Former Inclusion #8 (deleted) And 6.1 Former Inclusion #15 (now Inclusion #12)	Cohort 2 advanced (metastatic or unresectable) SS participants must have completed at least one standard of care treatment including anthracycline containing regimen OR is intolerant to the therapy. Participants who are not candidates to receive doxorubicin should have received ifosfamide unless also intolerant to or ineligible to receive ifosfamide. Participants who received neoadjuvant/adjuvant anthracycline or ifosfamide based therapy and progressed	Clarification on disease characteristics for inclusion of SS participants.

Section # and Name	Description of Change	Brief Rationale
	within 6 months with metastatic disease will be eligible.	
6.1 Former Inclusion #18 (now Inclusion #15)	Participants must have a predicted life expectancy that is ≥6 months (Inclusion #15)	Extension of projected life expectancy requirement because leukapheresis can now be performed earlier in treatment plan.
6.1 Former Inclusion #19 (now Inclusion #16)	Participants must have a Left ventricular ejection fraction ≥45% with no evidence of clinically significant pericardial effusion or as per institution's guidelines (Inclusion #16)	Clarification.
6.1 Former Inclusion #20 (now Inclusion #18) Table 9.	Participant must have adequate organ function and blood cell counts within 7 days prior to the day of leukapheresis, (or first day of lymphodepletion during Treatment fitness assessment), as indicated by the laboratory values in Table 9 (Inclusion #18 Clarification of Definitions of Adequate Organ Function: - ANC (must be obtained without G-CSF support) - CD3 count is no more an eligibility criterion - Platelets must be ≥100 $x10^9$/L - Renal function has been clarified based on participant age, and method - Albumin must be ≥3.5 g/dL - Footnote a) prohibits platelet transfusions accepted within 14 days from testing - Footnote b) prohibits red blood cell transfusions to meet minimum hematologic values for eligibility - Footnote c) clarifies reassessment conditions prior to lymphodepletion - Footnote d) references guideline on anticoagulant medication prior to lymphodepletion	Clarification.
6.1 Former Inclusion Criterion #21 (now Inclusion #19)	Clarify that contraception for male and female participants must be followed during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or until persistence of gene modified cells in the participant's blood is below the level of detection for 2 consecutive assessments, whichever is longer.	Clarification.

Section # and Name	Description of Change	Brief Rationale
6.2 Exclusion Criteria 6.2.2 Leukapheresis Eligibility Screening And 6.2.3 Treatment And Table 10 – Washout periods	Clarification of washout periods requirements prior to leukapheresis and prior to lymphodepletion.	Alignment with cell gene therapy program.
6.2 Exclusion Criteria Former Exclusion Criterion #2 (now Exclusion criterion #6) And Exclusion criterion #5 (deleted)	Clarification of CNS metastases exceptions for NSCLC participants. Removed restriction on maximum lines of therapy for NSCLC participants (former Exclusion criterion #5).	Broaden NSCLC patient eligibility
6.2 Former Exclusion Criteria #6 and 7 (now Exclusion criteria #3 and 4)	Per Section 6.3.5: - Added exception to exclusion of participants who have received prior genetically engineered NY-ESO-1 specific T cells, NY-ESO-1 vaccine or targeting antibody. - Added exception to participants who have received prior gene therapy using an integration vector.	Allow participants who have benefited from GSK3377794 (lete-cel) to be considered for treatment with GSK3901961 under conditions defined in Section 6.3.5.
6.3.4. Rescreening/Transfer (new section added)	Participants who were screenfailure/withdrawn prior to T-cell administration may be rescreened in the same study/substudy or transferred to any applicable GSK-sponsored study or substudy of this protocol. Rescreening, leukapheresis procedure or manufacture process may be waived after consultation with Sponsor.	To allow for re-allocation of participants onto other suited protocols/substudies when available, and for the possibility of skipping steps that have already been completed under the original comparable protocol, after consultation with Sponsor.
6.3.5. Potential eligibility of participants who have previously received letetresgene autoleucel	Participants who achieved a confirmed response of CR or PR or SD ≥3 months following first infusion of GSK3377794 (lete-cel) could possibly benefit post progression from receiving a second course of treatment with next generation NY-ESO-1 specific T cells (such as GSK3901961). Considerations will be made on a case by case basis. Rationale and minimal requirements are laid out in this section	To allow for possible future inclusion of prior lete-cel treated participants.

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

12.2 Amendment 02 (04 November 2021)

Amendment 02 - Date 04 November 2021

Overall Rationale for Amendment 02:

The primary rationales for protocol Amendment 02 are as follow:

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

2. For participants treated as of protocol amendment 02, the cyclophosphamide dose in the lymphodepleting chemotherapy was reduced on Day -7 thru Day -4 to further optimize and reduce potential for acute and prolonged cytopenias while also minimizing impact on efficacy

3. For NSCLC participants treated as of Protocol Amendment 02, the lymphodepleting chemotherapy schedule was changed from Day -8 through Day -5 to Day -7 through Day -4 to align with the schedule for the sarcoma participant cohort.

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

Section # and Name	Description of Change	Brief Rationale
Title page and throughout document	Replaced asset number GSK337794 with GSK3901961 as appropriate	Include asset number relevant to substudy 1 for GSK3901961
Title page and title page prior to Synopsis	Added “myxoid/round cell liposarcoma”	Acknowledge addition of MRCLS to participant population
Table of contents	Updated Table of Contents to refer only to substudy 1	Include Table of Contents relevant only to substudy 1 rather than to overall master protocol
Synopsis, Section 3.1 Background and Rationale, Section 4 Objectives and Endpoints, and throughout the protocol	Added MRCLS	Inclusion of myxoid/round cell liposarcoma (MRCLS) as a second translation-related sarcoma indication
Synopsis, Section 5.1 Overall Design – Figure 1	Added MRCLS to SS, corrected first panel in figure to state “Safety review after each 3 dosed participants”, and updated dose expansion text for duration of participant follow-up on study	Clarify content of patient population by incorporating MRCLS indicating that only dosed participants would be evaluated for safety, and clarifying that participants would remain in Interventional phase until PD or until end of Interventional phase, whichever is sooner.
Table 1 Schedule of Activities	Updated footer 6 to indicate that tobacco use is to be assessed for participants from all tumor types	Expand tumor type groups to be assessed for tobacco usage to all tumor types given all tumor types impacted by exposure to tobacco
Table 2 and Table 4 Schedule of Activities	Removed Days -8, -7, -6, and -5 from Day row in lymphodepletion column and left in place Days -7, -6, -5, and -4	Update to reflect that participants with any tumor type – including NSCLC – will undergo lymphodepletion on Day -7 through and including Day -4 as mandated by updated lymphodepletion regimen
Table 2, Table 3, Table 4, and Table 5 Schedule of A ctivities	Removed “-9 to” from Day row in Treatment Fitness and Eligibility / Baseline column	Update to reflect that participants with any tumor type – including NSCLC – will undergo lymphodepletion on Day -7 through and including Day -4 and will end on Day -8 rather than Day -9 as mandated by updated lymphodepletion regimen
Table 2 and Table 4 Schedule of Activities	Updated timing of creatinine clearance calculation from Month 12 to Month 18 and Month 30	Update for consistency with Study 208467 and for longer term monitoring of CrCl.
Table 2 Schedule of Activities	Updated superscript to footnote 34 given original footnote 34 was deleted	Correct relevant footnote number from 35 to 34

Section # and Name	Description of Change	Brief Rationale
Table 2 and Table 4 Schedule of Activities- Footnote 6	Updated footnote 6 to indicate that tobacco use is to be assessed for participants from all tumor types	Expand tumor type groups to be assessed to all tumor types given almost all tumor types impacted by exposure to tobacco
Table 2 and Table 4 Schedule of Activities Footnote 13	Updated footnote 12 to provide guidance on required additional cardiac monitoring in the event of CRS Grade ≥2	Implemented additional safety monitoring measures in accordance with a recent Dear Investigator Letter (21 OCT 2021) and safety events.
Table 2 and Table 4 Schedule of Activities Footnote 20	Updated footnote 19 to specify guidance for additional assessments for cardiac-compromised participant	Implemented additional safety monitoring measures in accordance with a recent Dear Investigator Letter (21 OCT 2021) and safety events.
Table 2 and Table 4 Schedule of Activities – Footnote 20 and Footnote 23	Updated footnote 20 and footnote 23 to include assessments of troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP)/ BNP – originally added in Protocol Amendment 01	Align footnote with laboratory assessment added in Protocol Amendment 01
Table 2 and Table 4 Schedule of Activities – Footnote 33 and Footnote 34	Updated footnote 33 to clarify timing of fludarabine for participants ≥60 years of age and with any tumor type Remove footnote 34 to clarify timing of cyclophosphamide for participants with synovial sarcoma or MRCLS	Align fludarabine dosing for patients ≥60 years of age with updated lymphodepletion schedule presented in this amendment Align guidance for cyclophosphamide dosing for synovial sarcoma and MRCLS participants with updated lymphodepletion schedule presented in this amendment
Table 2 and Table 4 Schedule of Activities	Removed abbreviations for non-small cell lung cancer and synovial sarcoma from abbreviation list at base of table	Remove abbreviations given no longer used in table due to updated lymphodepletion schedule
Table 3 and Table 5 Schedule of Activities Footnote 8 in each table	Updated acceptable timeframe (within 90 days of start of lymphodepletion)	Update 6 months to 90 days to optimize quality of Baseline tumor sample
Table 3 and Table 5 Schedule of Activities Footnote 11 in each table	Removed footnote 10	Remove footnote because Baseline stool sample will no longer be collected and microbiome analysis will not be performed
Table 6 Schedule of Activities Footnote 2	Updated footnote to describe time period for study assessments	Update footnote to clarify that assessments are to be conducted until disease progression
Table 6 Schedule of Activities Footnote 6	Updated to provide more complete description of AE/SAE collection	Update to better describe how AE/SAEs are to be reported during Years 6-15 post T-cell infusion and for consistency with guidance in Study 208750 for Long-term Follow-up

Section # and Name	Description of Change	Brief Rationale
Section 3.1.2 Synovial sarcoma	Removed text describing olaratumab from list of possible potential first-line treatment Added text describing frequency of NY-ESO- expression in synovial sarcoma and unmet need for new therapies	Update to remove drug that was withdrawn by manufacturer Update rationale for evaluating participants with synovial sarcoma in this substudy with GSK3901961
Section 3.1.3 Myxoid/round cell liposarcoma	Added new section describing MRCLS as well as therapy options for MRCLS	Add relevant information needed to support inclusion of MRCLS
Section 3.1.4 Non-small cell lung cancer	Streamlined text describing therapies for metastatic NSCLC.	Streamline lengthy section to improve readability
Section 3.2.1 Risk Assessment	Updated safety data throughout section	Update safety data for lete-cel using Investigator's Brochure Version 13 as the reference.
Section 3.2.1 Risk Assessment	Updated description for binding of lete-cel to peripheral nerves	Provide update on binding of lete-cel to peripheral nerves to more completely describe the potential for nervous system binding / adverse effects
Section 3.2.1 Risk Assessment Table 7	Updated risk mitigation information including visual impairment, fatal cardiac arrest, and hemorrhage secondary to thrombocytopenia	Update table to accurately present most recent key safety data particularly as addressed in the Dear Investigator Letter (21 October 2021)
Section 3.2.2 Benefit Assessment	Updated total enrollment as of 27 Jan 2021. Updated reference for efficacy results from Study 208469.	Provide up-to-date efficacy data for all relevant studies
Section 3.2.3 Overall Benefit Risk Conclusion	Updated risk frequencies for CRS and ICANS	Provide up-to-date risk data for two key adverse events of special interest to best inform investigators and site staff
Section 4 Objectives and Endpoints	Updated primary, secondary, and exploratory objectives to include MRCLS in Cohort 2	Update relevant participant description to reflect inclusion of MRCLS plus the original synovial sarcoma and NSCLC

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Overall Design and Figure 1	Added MRCLS as tumor type to be studied Clarified that participants from Cohort 1 and 2 could enroll into Dose Confirmation phase.	Add MRCLS as additional tumor type in Cohort 2 as a second translation-related sarcoma indication. Clarify that participants from either of the 2 cohorts may enroll into the Dose Confirmation phase. For Figure 1: Incorporate MRCLS to acknowledge addition of MRCLS to participant population, indicate that only dosed participants would be evaluated for safety, and clarify that participants would remain in Interventional phase until PD or until end of Interventional phase, whichever is sooner
Section 5.1.1.2 Determining the RP2D	Updated details on statistics associated with determination of recommended Phase 2 dose (RP2D)	Further describe use of Modified Toxicity Probability Interval statistics approach to determining RP2D
Section 5.1.2 Dose Expansion Phase	Increased flexibility in inclusion (or not) of sentinel patients in primary efficacy analysis	Replace “will” with “may” in the sentence “The primary analysis will assess safety, efficacy, pharmacokinetic, and pharmacodynamic data and may include the sentinel patient who received a split dose provided they received the RP2D dose.”
Section 5.1.3 Participant Journey	Updated Figure 3 to include Cohort 3 Screening: Added MRCLS as tumor type to be evaluated. Added guidance on acceptable age for tumor samples used in target screening for antigen Added guidance on which tumor type a participant may have and be eligible for enrollment Added guidance on required participant status prior to leukapheresis	Update visual guide to the patient screening and treatment journey via Figure 3. Add additional information for acceptable tumor age for antigen screening and acceptable participant tumor type.
Section 5.1.3 Participant Journey Part 1 Screening	Included third option of target expression screening	Added option of proceeding with tumor sample collection based on a positive local HLA result.
Section 5.1.4 Tumor Biopsies	Updated timing for acceptable age of fresh biopsy from target expression screening for use as the Baseline biopsy	Clarify window within which fresh biopsy obtained at target expression screening may be used also as the Baseline tumor sample in order to optimize tumor sample quality

Section # and Name	Description of Change	Brief Rationale
Section 5.4.Justification for Population	Included efficacy data from Study 208469.	Provide GSK3377794 (lete-cel) efficacy data from Study 208469 to support inclusion of MRCLS in participant population
Section 5.5.1 Dosing Rationale	Added sentence describing potential reduced dose range	Provide details of dose range to be evaluated if reduction of original dose range is required
Section 5.5.2 Justification of Lymphodepletion Regimen	Replaced original text with text describing refined lymphodepleting regimen	Provide rationale for changing dose and dosing schedule for fludarabine and cyclophosphamide relative to those used in prior and ongoing studies
Section 6.1.1 Inclusion Criterion 3	Added LAGE-1a	Include LAGE-1a in antigen testing scenario to open possibility of enrolling LAGE-1a-positive participants once a central laboratory assay becomes available.
Section 6.1.1 Target Expression Screening Inclusion Criteria	Updated requirements for determination of correct synovial sarcoma diagnosis Added requirements for eligibility for SS and MRCLS	Clarified histologic and other requirements (e.g., specific translocations, mutations) that must be met for a participant with a particular tumor type to be eligible for substudy 1
Section 6.1.2 Leukapheresis Eligibility Screening Inclusion Criteria	Updated or added required prior therapies for all tumor types evaluated in substudy 1	Provide clear guidance on required prior therapy in order for participant with a given tumor type to be eligible for substudy 1
Section 6.1.2 Leukapheresis Eligibility Screening Inclusion Criteria Table 9	Corrected required hemoglobin level to ≥8 g/dL or 5.0 mmol/L (not achieved by transfusion)	Clarify required adequate organ function parameters for hemoglobin and creatinine clearance for all participants
Section 6.1.2 Criterion 9 and Section 6.3.4 Screening Under Other GSK Studies	Updated to indicate acceptability of LAGE-1a positive participants	In order to accommodate participants from other studies whose tumor was positive for LAGE-1a and to facilitate study-to-study transfer of these participants
Section 6.1.2 Leukapheresis Eligibility Screening Inclusion Criteria	Updated contraception criterion for times of use for males and females	Clarify contraception use start times for males and females relative to start of lymphodepletion
Section 6.1.3 Treatment Eligibility Screening Inclusion Criteria	Updated disease progression criterion concerning previously irradiated lesions	Clarify that previously irradiated but progressing lesions may be used to demonstrate disease progression prior to lymphodepletion

Section # and Name	Description of Change	Brief Rationale
Section 6.2.1 Target Expression Screening Exclusion Criteria 3 and 5	Updated exclusion criteria for prior treatment with NY-ESO-1-specifc assets and for prior gene therapy with integrating vector	Add that participants previously treated with lete-cel may receive GSK3901961 if they have met certain criteria
Section 6.2.2 Leukapheresis Eligibility Screening Exclusion Criteria	Updated exclusion criterion for NSCLC participants with treated asymptomatic CNS metastases	Add 3 additional criteria – all pertaining to various radiotherapy washout periods – to further describe those participants with asymptomatic CNS metastases who might be considered to be eligible for enrollment Further enhanced safety requirements for specific NSCLC participants with CNS metastases by mandating that CNS metastases appear stable via repeat MRI prior to lymphodepletion.
Section 6.2.2 Leukapheresis Eligibility Screening Exclusion Criteria	Updated testing criteria for Epstein Barr virus (EBV) and cytomegalovirus	Align testing requirements with those of rest of NYESO program
Section 6.2.2 Leukapheresis Eligibility Screening Exclusion Criteria	Update lung and heart radiotherapy exclusion criterion	Clarify that exclusion criterion is not specific to participants with NSCLC, clarify required washout period for low dose radiotherapy to lung/mediastinum.
Section 6.2.3 Treatment Eligibility Exclusion Criteria	Update exclusion criterion for situation in which all measurable lesions have been irradiated	Clarify that an irradiated measurable lesion with unequivocal progression after radiotherapy may be considered a target lesion regardless of time since last radiotherapy dose.
Section 6.2.3 Treatment Eligibility Exclusion Criteria	Moved exclusion criterion for lung radiotherapy specifications from Leukapheresis Exclusion Criteria to Treatment Eligibility Exclusion Criteria (now Exclusion Criterion 22)	Clarified that exclusion of prior radiotherapy is relevant prior to lymphodepletion but not prior to leukapheresis
Section 6.3.4 Screening Under Other GSK Studies	Added section on potential to enroll participants previously screened or enrolled in other GSK studies	Clarify that participants previously screened or enrolled under other GSK studies may be enrolled in Substudy 1 of Study 209012 acknowledging the potential need for repeat HLA, antigen or clinical testing.
Section 7.1.3 Lymphodepleting Chemotherapy	Updated section to present a single lymphodepleting regimen. Removed text specific to NSCLC. updated Table 11 to present changes to lymphodepletion doses and dosing schedule, and removed Table 12.	Present changes to lymphodepletion regimen unifying regimen across all tumor types and addressing safety concerns about prolonged cytopenias

Section # and Name	Description of Change	Brief Rationale
Section 7.1.3 Lymphodepleting Chemotherapy	Updated footnote to fludarabine dose adjustment table	Clarify that creatinine clearance (CrCl) in mL/min values to be used in fludarabine dose adjustment table and exact steps to be followed to obtain this CrCl value
Section 7.5.1 Prohibited Concomitant Medication and Treatment	Updated language for prohibited therapies	Clarify that all listed therapies are anti-cancer therapies and are prohibited
Section 7.5.1 Prohibited Concomitant Medication and Treatment	Removed sentence “If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required.”	Remove sentence that is not relevant to GSK3901961 single dose (or at most split dose) therapy
Appendix 11 References	Updated to only include references for Substudy 1	In support of protocol modularization, references list was updated to include only those references relevant to Substudy 1.

12.3 Amendment 03 (20 December 2021)

Amendment 03 – Date 20 December 2021

Overall Rationale for Amendment 03:

Finalize splitting of document from Master protocol Amendment 02 as independent Substudy 1 document. Please refer to Core Section 12.13 for Master Protocol Document History.

Minor typo corrections throughout document.

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