TITLE PAGE

Protocol Title: A Phase 1b/2a Pilot Study to Evaluate the Safety and Tolerability of Autologous T-Cells Expressing Enhanced TCRs (T-Cell Receptors) Specific for NY-ESO-1/LAGE-1a (GSK3377794) Alone, or in Combination with Pembrolizumab in HLA-A2+ Participants with NY-ESO-1- or LAGE-1a-Positive Advanced or Recurrent Non-Small Cell Lung Cancer

Protocol Number: 208471 / Amendment 07

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

Study Phase: Phase 1b/2a

Short Title: Pilot immunotherapy study with letetresgene autoleucel (lete-cel, GSK3377794) T-Cells in NY-ESO-1/LAGE-1a-positive advanced NSCLC either alone or in combination with pembrolizumab.

Sponsor Name and Legal Registered Address:

GlaxoSmithKline LLC
5 Crescent Drive
Philadelphia, PA 19112
US

Medical Monitor Name and Contact Information: To be provided separately OR can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s):

IND: 14603

EudraCT: 2018-003949-42

Approval Date: 04-NOV-2021

SPONSOR SIGNATORY:

Protocol Title: A Phase 1b/2a Pilot Study to Evaluate the Safety and Tolerability of Autologous T-Cells Expressing Enhanced TCRs (T-Cell Receptors) Specific for NY-ESO-1/LAGE-1a (GSK3377794) Alone, or in Combination with Pembrolizumab in HLA-A2+ Participants with NY-ESO-1- or LAGE-1a-Positive Advanced or Recurrent Non-Small Cell Lung Cancer

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Date

The signed page is a separate document

Medical Monitor Name and Contact Information refer to Study Reference Manual

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 07	04-NOV-2021	TMF-14132100
Amendment 06-GBR-2	21-JUL-2021	TMF-13894889
Amendment 06-NET-2	19-MAY-2021	TMF-13775495
Amendment 06-GBR-1	19-MAY-2021	TMF-13775509
Amendment 06-SPA-1	19-MAY-2021	TMF-13775486
Amendment 06	17-MAY-2021	TMF-12466596
Amendment 05-NET-1	27-MAR-2020	2018N358002_11
Amendment 05-UK-1	26-MAR-2020	2018N358002_10
Amendment 05-SPA-1	26-MAR-2020	2018N358002_09
Amendment 05	21-FEB-2020	2018N358002_08
Amendment 02-NET-1	29-OCT-2019	2018N358002_07
Amendment 04	29-OCT-2019	2018N358002_06
Amendment 03	01-OCT-2019	2018N358002_05
Amendment 02-SPA-1	16-SEP-2019	2018N358002_04
Amendment 02-UK-1	03-SEP-2019	2018N358002_03
Amendment 02	13-FEB-2019	2018N358002_02
Amendment 01	17-OCT-2018	2018N358002_01
Original Protocol	11-JUL-2018	2018N358002_00

Amendment 07: 04-NOV-2021

Overall Rationale for the Amendment:

The overall rationale for this amendment is to:

- Implementation of additional safety monitoring measures in accordance with a recent Dear Investigator Letter and safety events for lete-cel.
- For participants treated as of protocol amendment 7, the upper end of the target dose range of transduced T cells was increased from to 8×10^9 to 15×10^9 in order to maximize the delivery of cells for participants whose manufacture yields $>8\times10^9$ transduced T cells.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Made administrative changes and corrected clerical errors.	For clarity and consistency
Section 1.1 Synopsis Section 4.3.2 Justification of Lete-cel dose Section 6.4.2 Lete-cel dose	The upper end of the lete-cel dose was expanded from 8×10^9 transduced T cells to 15×10^9 transduced T cells for participants treated under protocol amendments 7 and beyond. In Section 4.3.2, added justification of changed lete-cel dose	The lete-cel dose range was expanded in order to maximize the use of cells in participants whose manufacture yields $>8\times10^9$ transduced T cells.
Section 1.3 Schedule of Activities (SoAs)	Modified time window for the assessment of infectious disease markers: must be completed within 28 days prior to leukapheresis (Table 2, Note 16) Added thyroid function tests to the Schedule of Activities in Part 4 (Table 5) Clarified that brain MRI prior to lymphodepletion would need to show stability/reduction of CNS metastases if radiotherapy was administered after the MRI performed prior to leukapheresis (Table 3, footnote 13) Clarified that CMV infection will be assessed if GBS is suspected (Table 3, footnote 17) EoT visit is to be completed by participants who withdraw from the interventional phase and have not withdrawn from the study. If EoT assessments are completed sooner than what is indicated in Table 7, only need to repeat assessments not performed as part of the last visit. (Table 7, Note 1.)	In alignment with relevant regulations [Implementing Directive 2004/23/EC, 2006] For accuracy For participant safety For participant safety and in alignment with other protocols across the lete-cel program In alignment with changes in Section 4.4.1

Section # and Name	Description of Change	Brief Rationale
	Added information about ECHO/MUGA at onset of Grade ≥2 CRS, about continuous cardiac telemetry monitoring (per Section 10.9.5) and cardiologist evaluation in participants with increased burden of cardiovascular risk factors (per Section 8.2.3). (Table 3, Footnotes 9 and 10, respectively)	In alignment with changes incorporated into Section 10.9.5 and Section 8.2.3, respectively
Section 2.3.1 Risk Assessment	Added risks of cardiac arrest and haemorrhage secondary to thrombocytopenia Updated information for risk of ICANS	In accordance with a recent Dear Investigator Letter and safety events for lete-cel
Section 4.4.1 End of Interventional Phase/Study for Individual Participants	Added language to clarify the difference between end of interventional phase and end of study for individual participants (in alignment with incorporation of Part 5 in protocol amendment 6)	For clarity, since end of intervention and end of study for individual participants might vary now that study includes Part 5
Section 5.2 Exclusion Criteria	Modified language on treatments not permitted prior to the study Under active infection, added a sub-bullet for active CMV infection Included additional details under CNS metastases exclusion criterion Moved exclusion criterion, about radiotherapy that involves lung or mean heart dose >20 Gy, from prior to leukapheresis to prior to lymphodepletion to meet intent of criterion and eliminate unnecessary burden to patient. Added clarifying language on radiotherapy exclusion criterion, intent has not changed. Modified text in exclusion criterion concerning irradiated measurable lesions, intent has not changed. Moved note to exclusion criterion #19, due to relevance.	For clarity / accuracy, in alignment with other protocols across the lete-cel program For clarity and accuracy, this sub-bullet was missing For participant safety For clarity, to eliminate redundancy For clarity
Section 5.2 Exclusion Criteria Section 10.9.2 Infection Sectionn 10.9.2.6 Other Anti-Microbial Prophylaxis/Treatment	Included additional information on existing exclusion criterion to exclude participants with ongoing systemic fungal infections Added information on surveillance for indwelling central lines (Section 10.9.2) and risk of cardiac toxicity with use of anti-microbial treatments (Section 10.9.2.6)	For participant safety

Section # and Name	Description of Change	Brief Rationale
	Added recommendations in case of prolonged leukopenia or gross hematuria (Section 10.9.2.6)	
Section 6.3 Lymphodepleting Chemotherapy and Section 10.9.10 Lymphodepleting Chemotherapy Symptom Management	Use of prophylactic G-CSF should be *approximately* 24 hours after last dose of chemotherapy	At investigator's discretion and in alignment with other lete-cel protocols
Section 6.9.1 Prohibited Concomitant Medication and Treatment	Clarified language on the administration of locoregional therapies during the interventional portion of the study. Eliminated the following sentence due to redundancy: "Exceptions to the above rule can be made if a participant has progressive disease and cannot be treatment-free"	For clarity For clarity, redundant language
Section 8.2.3 Cardiac Assessments	This section was revised to include a definition of participants with increased burden of cardiovascular risk. Those participants with increased burden are required to undergo a cardiology evaluation prior to lymphodepletion and continuous cardiac telemetry for a minimum of 3 days post T-cell infusion (moved from earlier portion of Section 8.2.3)	This revision was made to mitigate cardiac complications in participants with high risk factors
Section 8.2.4 Pulmonary Assessments (New Section)	This section recommends pulmonary consultation for any participant with any history or known lung metastases. Also, closer monitoring is recommended for at least 3 days post T-cell infusion and in case of suspected CRS and should include frequent chest radiograms, fluid balance monitoring and continuous cardiac telemetry. Participants with compromised airway should be assessed prior to lymphodepletion (consider speech and swallow evaluation, as well as anaesthesia consult)	This section was added to recommend pulmonary assessments for participants with known lung metastases (active or previously treated)
Section 8.3.5 Testing for Persistence of Transduced T cells and Insertional Oncogenesis	Participants with a persistence of transduced T cells at first instance of >1% PBMCs and who have already been tested for Integration Site Analysis with a result of 'polyclonal', will only be retested if:	Clarify conditions for monitoring and retesting of participants who have already been tested for Integration Site Analysis with a result of 'polyclonal'

Section # and Name	Description of Change	Brief Rationale
	persistence of transduced T cells has suddenly increased; OR in case of suspected/reported hematological malignancy Added "In all cases of SAE that occur after T cell infusion, a transgene copy (persistence) sample must be obtained if feasible."	For safety purposes and in alignment with other lete-cel protocols
Section 1.3 Schedule of Activities (Table 4 and 6) Section 8.9 Biomarkers	Removal of plan to collect stool sample to assess gut microbial community; deleted Section 8.9.9: Stool Collection for Microbiome Analysis Removal of plan to investigate cell free RNA	Assays deprioritized
Section 9.2 Sample Size Determination	Change in sample size language to clarify that the study aims to enrol approximately 18 patients per arm to dose approximately 15 patients per arm.	For clarity
Section 9.2 Sample Size Determination	Clarified that participants to be included in statistical analyses need to meet "evaluable" criteria, as indicated in Section 9.3	For clarity
Section 10.9.2.3 Cytomegalovirus	Clarified that CMV screening will happen at study entry and at baseline	Correction for accuracy, in alignment with Schedule of Activities
Section 10.9.3 Hematologic and Blood Support	Clarified that blood support should be provided to maintain platelets $>10 \times 10^9$/L in the in-patient and $>20 \times 10^9$/L in the out-patient settings. Made small modifications to existing language to indicate: or as clinically indicated in the judgement of the Investigator, or in accordance with institutional practice.	For clarity and safety purposes
Section 10.9.5 Management of Cytokine Release Syndrome	Participants with increased cardiovascular risk factors (per Section 8.2.3) might need earlier intervention with tocilizumab and/or steroids at the onset of CRS. If CRS ≥Grade 2 is suspected, an ECHO/MUGA is required at onset If CRS ≥Grade 2, additional monitoring should include: • Continuous cardiac telemetry monitoring • ECHO/MUGA as clinically indicated • Local tests	Section was revised to specify management of patient with an increased burden of cardiovascular risk factors

Section # and Name	Description of Change	Brief Rationale
	○ Daily troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) or BNP tests Added language on organ toxicity grade per CTCAE V5.0, in alignment with Section 10.3.4.	For clarity and in alignment with Section 10.3.4

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1b/2a Pilot Study to Evaluate the Safety and Tolerability of Autologous T-Cells Expressing Enhanced TCRs (T-Cell Receptors) Specific for NY-ESO-1/LAGE-1a (GSK3377794) Alone, or in Combination with Pembrolizumab in HLA-A2+ Participants with NY-ESO-1- or LAGE-1a-Positive Advanced or Recurrent Non-Small Cell Lung Cancer

Short Title: Pilot immunotherapy study with letestregene autoleucel (lete-cel, GSK3377794) T-Cells in NY-ESO-1/LAGE-1a-positive advanced NSCLC either alone or in combination with pembrolizumab.

Rationale: Adoptive T-cell therapy (ACT) is a therapeutic approach that uses a cancer patient's own T lymphocytes obtained by leukapheresis, engineered to express a tumor-specific T-cell receptor (TCR), expanded *ex vivo,* and re-infused into the patient, with the aim of generating an anti-tumor T-cell immune response. New York esophageal squamous cell carcinoma 1 (NY-ESO-1) and cancer testis antigen 2 (LAGE-1a) antigens are tumor-associated proteins that have been found in several tumor types, including non-small cell lung cancer (NSCLC). Previous clinical trials using ACT with T-cells directed against NY-ESO-1/LAGE-1a have shown objective responses between 40% to 60% in participants with synovial sarcoma, metastatic melanoma, and multiple myeloma.

Pembrolizumab is a monoclonal antibody that acts specifically on tumor-targeting T-cells to block programmed death protein 1/programmed death protein 1 ligand (PD-1/PD-L1) interaction and increase T-cell anti-tumor function; pembrolizumab will be used in combination with NY-ESO-1/LAGE-1a TCR engineered patient T-cells, lete-cel, to potentially further improve therapy for patients.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of autologous genetically modified T-cells (lete-cel) in human leukocyte antigen (HLA) 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 advanced NSCLC alone [Arm A] or lete-cel in combination with pembrolizumab in participants with NSCLC lacking actionable genetic aberrations [Arm B] and participants with NSCLC with an actionable genetic aberration [Arm C]	• Frequency and severity of AEs, serious adverse events (SAEs) and AEs of special interest (AESIs; as defined in protocol) • AE/SAEs leading to dose delays and/or withdrawals in participants who received lete-cel alone or in combination with pembrolizumab
• To determine the response to lete-cel alone [Arm A] or lete-cel in combination with pembrolizumab in participants with NSCLC lacking actionable genetic aberrations [Arm B] and participants with NSCLC with actionable genetic aberrations [Arm C]	• Overall Response Rate (ORR) (investigator assessed according to RECIST v1.1)

Objectives	Endpoints
Secondary - Efficacy	
• To further investigate the anti-tumor activity of lete-cel alone or lete-cel in combination with pembrolizumab according to RECIST v1.1 criteria	• Progression-Free Survival (PFS) • Disease Control Rate (DCR) • Duration of Response (DoR) • Time to Response (TTR)
Secondary - Pharmacokinetics	
• To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 specific (c259) T cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to time t AUC(0-t), as data permit

CCI

[redacted]

Abbreviations:
CCI; AE = adverse event/s; AESI = adverse event of special interest; ALK/ROS1 = anaplastic lymphoma kinase/c-ros oncogene 1; AUC(0-t) = area under the time curve from zero to time t; Cmax = maximum persistence; CRS = cytokine release syndrome; DCR = disease control rate; DoR = duration of response (iDoR = DoR based on CCI); ECG = electrocardiogram; ECOG PS = Eastern Co-operative Oncology Group performance status; eCRF = electronic case report form; EGFR = epidermal growth factor receptor; FDG = fluorodeoxyglucose; G-CSF = granulocyte colony stimulating factor; HLA = human leukocyte antigen; IL = interleukin; CCI CCI AGE-1a = cancer testis antigen 2; NSCLC = non-small cell lung cancer; NY-ESO-1 = New York esophageal squamous cell carcinoma 1; ORR = overall response rate (CCI); CCI CCI; PET = positron emission tomography; PFS = progression-free survival CCI RECIST = Response Evaluation Criteria In Solid Tumors CCI); CCI; SAE = serious adverse event; TCR = T-cell receptor; CCI Tmax = time to Cmax; CCI; TTR = time to response; WT = wild-type.

Overall Design:

This is a multi-arm, open-label study of letestregene autoleucel (lete-cel, GSK3377794) in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive adults whose tumors express NY-ESO-1 and/or LAGE-1a.

This study will enroll participants who have unresectable Stage IIIb or Stage IV NSCLC and also fit criteria outlined in eligibility.

Disclosure Statement:

This is a multi-cohort, open-label, expansion cohort study with 3 arms whose primary purpose is to evaluate clinical activity and safety for each arm.

Number of Participants:

Approximately 54 participants will be enrolled to achieve at least 15 evaluable participants per arm. At least 30 participants (15 per each arm) with NSCLC lacking actionable genetic aberrations will be assigned to lete-cel alone (Arm A) or in combination with pembrolizumab (Arm B). Assignment of participants to Arm A or B will be determined by the Sponsor and will be assigned to Arm A first and then to Arm B.

At least 15 evaluable participants with NSCLC with an actionable genetic aberration (e.g. BRAF, ALK/ROS1 or any other per NCCN guidelines) will be assigned to treatment with lete-cel in combination with pembrolizumab (Arm C). Participants with actionable genetic aberrations may receive treatment as part of Arm C only following treatment with targeted standard of care therapy (NCCN or or equivalent country-guidelines (e.g., ESMO, NICE, etc.), as applicable).

Intervention Groups and Duration:

In Arm A, lete-cel will be administered as a single intravenous (IV) infusion of 1 to 15 x 10^9 transduced cells. There will be no re-treatment with lete-cel in this study. Participants who subsequently progress may optionally receive therapy with pembrolizumab 200 mg once every 3 weeks (Q3W) for up to 35 cycles, until disease

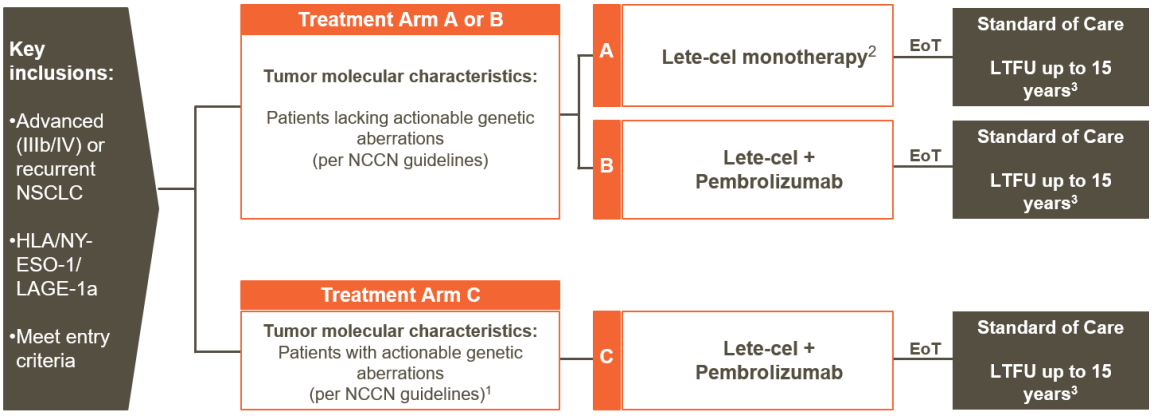
progression or until early withdrawal, at which point participants will then be entered into a separate long-term follow-up (LTFU) protocol (GSK Study 208750).

In Arms B and C, participants will receive a single IV infusion of lete-cel on Day 1 followed by pembrolizumab 200 mg starting on Day 22 (Week 4 Day 1). Pembrolizumab will be administered for up to 35 cycles Q3W, until disease progression or until early withdrawal, at which point participants will be entered into the LTFU protocol (GSK Study 208750). If not yet enrolled in the LTFU protocol, participants will be followed per LTFU schedule under this protocol (Part 5) until enrolled in LTFU protocol.

Data Monitoring Committee: No

1.2. Schema

Figure 1 Study Schema



Abbreviations: ALK/ROS1 = anaplastic lymphoma kinase/c-ros oncogene 1; BRAF = B-Raf; EGFR = epidermal growth factor receptor; EoT = end of treatment; HLA = human leukocyte antigen; LAGE-1a = cancer testis antigen 2; NCCN = National Comprehensive Cancer Network; NSCLC = non-small cell lung cancer; NTRK = Neurotrophic Tropomyosin-Related Kinase; NY-ESO-1 = New York esophageal squamous cell carcinoma 1; PD-1 = programmed death protein 1; PD-L1 = PD-1 ligand; LTFU = long-term follow-up.

1. NSCLC patients with an actionable genetic aberration may receive treatment as part of Arm C only following treatment with targeted standard of care therapy (NCCN or equivalent country guidelines (e.g., ESMO, NICE, etc.), as applicable).
2. Option of pembrolizumab therapy at time of disease progression following Lete-cel administration and based on benefit-risk evaluation with Sponsor's Medical Monitor (or designee) approval.
3. LTFU requires participant enrollment in a dedicated LTFU protocol (GSK Study 208750). If not yet enrolled in the LTFU protocol, participants will be followed per LTFU schedule under this protocol (Part 5) until enrolled in the separate LTFU protocol (see Table 8).

1.3. Schedules of Activities (SoAs)

Table 2 Schedule of Activities – Screening (Part 1) and Leukapheresis (Part 2)

	Screening Phase[1]		Leuka-pheresis[4]	Notes
Day (D) / Week (W)	**Target Expression Screening[2]**	**Leukapheresis Eligibility Screening (Within 42 days prior to Leukapheresis)[3]**		
Informed Consent for Screening	X			1. Written informed consent must be obtained prior to performing any study assessments or procedures, except for those collected as SoC and considered acceptable for the study (footnote 11) or as part of other GSK studies (per Section 4.1.1). 2. Target Expression Screening may be performed under a separate protocol, if applicable, per Section 4.1.1. 3. Participants must be HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1/LAGE-1a positive tumor prior to conducting leukapheresis eligibility screening procedures. 4. Participants must meet all eligibility requirements prior to leukapheresis, as specified in Section 5. 5. If an archival tumor specimen is not available, then a fresh tumor tissue biopsy may be considered at the discretion of the investigator. See Section 8.9.2. 6. Only collect this sample if optional Liquid Biopsy Consent has been signed by the participant as part of the Informed Consent for Screening. Sample may be collected any time from signature of optional consent until leukapheresis. 7. Medical history will be recorded in the eCRF at Target Expression Screening and at Lymphodepletion Screening/Baseline visits; however, any changes in medical history must be recorded in source documents throughout the conduct of the study. 8. Includes all prescriptions, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported.
Informed Consent for Leukapheresis and Treatment		X		
Inclusion/Exclusion for Screening	X			
Inclusion/Exclusion for Leukapheresis		X		
Demographics	X			
HLA -A*02:01, A*02:05 and A*02:06 genotyping[1]	X			
Tumor expression of NY-ESO-1/ LAGE-1a[5]	X			
Liquid Biopsy (blood)[6]	X			
Medical History[7]	X	X		
Prior/Concomitant Medications[8]	X	X	X	
ECOG	X	X		
Physical Exam[10]		X		
Vital Signs / Height / Weight[15]		X		
12-lead ECG[9]		X		
ECHO/MUGA[11]		X		
CT / MRI[11,12]		X		
Brain MRI[11]		X		
Lymphocyte Subset (CD3/CD4/CD8)[10,11,13]		X		
Hematology[10,11]		X		

	Screening Phase[1]		Leuka-pheresis[4]	Notes
Day (D) / Week (W)	**Target Expression Screening[2]**	**Leukapheresis Eligibility Screening (Within 42 days prior to Leukapheresis)[3]**		
Clinical Chemistry[10,11]		X		9. Collect a single ECG. If QTc is >480 msec, collect 2 more ECGs 5 minutes apart and use the average of those QT values to determine eligibility. If the average QTc is >480 msec, obtain a manual overread of the triplicate. 10. All clinical assessments required at Leukapheresis Eligibility Screening must be performed within 42 days prior to leukapheresis, except for vital signs, weight, lymphocyte subset (CD3/CD4/CD8), hematology, clinical chemistry, coagulation tests, physical exam and urinalysis which must be done within 7 days prior to leukapheresis. 11. ECHO/MUGA, CT/MRI scan, brain MRI and laboratory assessments performed as standard of care prior to study consent will be acceptable as long as assessment is done within required time period before leukapheresis. 12. Any FDG PET/CT performed as part of clinical routine within the required time period before leukapheresis will also be collected centrally but will not replace CT scans. 13. CD3 count prior to leukapheresis should be preferably performed within 24 hours from leukapheresis procedure. 14. WOCBP must have a negative urine or serum pregnancy test at Screening and again prior to leukapheresis. 15. Includes temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. Height will be collected at the Screening visit only. FEV1, FVC, TLC, and DLCO will be measured to determine eligibility as described in Section 5. 16. Includes HIV, HBV, HCV, HTLV, EBV, CMV, and syphilis (spirochete bacterium). Must be completed within 28 days prior to leukapheresis. Testing is required at Screening and needs to be repeated at Baseline (see Table 3) to satisfy eligibility criteria. 17. Adverse events (AEs) should be collected and reported as noted in Section 8.4. 18. Arm assignment should occur before leukapheresis.
Coagulation Tests[10,11]		X		
Pregnancy Test[14]		X[14]	X[14]	
Urinalysis[10,11]		X		
PFTs[15]		X		
Infectious Disease Markers[11,16]		X		
Creatinine clearance by GFR or 24-h Urine Collection		X		
Adverse Events[17]	X	X	X	
Leukapheresis[18]			X	

Abbreviations: CMV = cytomegalovirus; CT = computed tomography; DLCO = pulmonary diffusing capacity for carbon monoxide; EBV = Epstein-Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FDG PET = fluorodeoxyglucose positron emission tomography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; HTLV = human T lymphotropic virus; LAGE-1a = cancer testis antigen 2; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NY-ESO-1 = New York esophageal squamous cell carcinoma 1; PFT = pulmonary function test; SoC = standard of care; TLC = total lung capacity; WOCBP = women of child-bearing potential.

Table 3 Schedule of Activities – Lymphodepletion/Treatment (Interventional Phase) (Part 3)

	Base-line	Lymphodepletion				Lete-cel Infusion[1]	Post-T-cell Infusion											
Day (D) / Week (W)	**Day -17 to -9**	**Day**					**Week[2]**											
		-8	**-7**	**-6**	**-5**	**1**	**2**	**3**	**4**	**5**	**2**	**3**	**4**	**5**	**6**	**7**	**10 to 25 Q3W**	**Arm A: 34-106 Q12W Arms B & C: 28-106 Q3W**
Visit Window	**n/a**					**n/a**	**±1 day**				**±3 days**						**±3 days**	
Treatment Fitness and Lymphodepletion Eligibility Screening[3]	X																	
Med. History[4]	X																	
Physical Exam	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological assessments[5]	X					X	X	X	X	X	X	X	X	X	X	X	X	X
ICE[5]						X	X	X	X	X	X							
Prior/Concomitant Medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X					X					X	X	X	X	X	X	X	X
Vital Signs[7,8]	X					X[8]	X	X	X	X	X	X	X	X	X	X	X	X
ECHO/MUGA[9]	X																	
12-lead ECG[10]	X					X			X		X							
Body CT/MRI[11,12]	X[11,12]					See footnotes 11 and 12												
RECIST evaluation	X[11]					See footnote 11												
Brain MRI[13]	X[13]					See footnote 13												
Chest X-Ray	X																	
Hematology[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ferritin[15]	X																	
Troponin and NT-proBNP/BNP[15]	X																	
Coagulation Tests[14,15]	X					X	X	X	X	X	X	X						

	Base-line	Lymphodepletion				Lete-cel Infusion[1]	Post-T-cell Infusion											
Day (D) / Week (W)	Day -17 to -9	Day									Week[2]							
		-8	-7	-6	-5	1	2	3	4	5	2	3	4	5	6	7	10 to 25 Q3W	Arm A: 34-106 Q12W Arms B & C: 28-106 Q3W
Visit Window	n/a					n/a	±1 day				±3 days						±3 days	
Pregnancy Test[16]	X[16]					X[16]							X			X	X	X
Urinalysis	X																	
Infectious Disease Markers (HIV, HBV, HCV, HTLV, EBV, and syphilis)	X																	
CMV IgG and PCR[17]	X					X					X		X		X	X		
TSH with Free T4[18]	X	See footnote 18																
CRP[15]	X					X			X		X	X	X	X	X	X	X	X
Uric Acid	X					X												
GFR or 24-h urine collection[19]	X																	
Adverse Events[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vector Copies (Persistence) for Safety (blood)[21]	X						For collection, see footnote 21											
VSV-G DNA (RCL) for Safety (blood)[22]	X						For collection, see footnote 22											
Lymphodepletion																		
Fludarabine		X	X	X	X													
Cyclophosphamide			X	X	X													
Investigational Product Administration																		
Lete-cel						X[23]												
Pembrolizumab	See footnote 24																	
See Table 4 for PK, Immunogenicity, and Biomarkers Samples																		
Genetic sample	X[25]																	
CCI [redacted]																		

	Base-line	Lymphodepletion				Lete-cel Infusion[1]	Post-T-cell Infusion											
Day (D) / Week (W)	Day -17 to -9	Day									Week[2]							
		-8	-7	-6	-5	1	2	3	4	5	2	3	4	5	6	7	10 to 25 Q3W	Arm A: 34-106 Q12W Arms B & C: 28-106 Q3W
Visit Window	n/a					n/a	±1 day				±3 days						±3 days	
CCI [redacted]																		

Abbreviations:
AE = adverse event; BNP = B-type natriuretic peptide; CMV = cytomegalovirus; CRP = C-reactive protein; CRS = cytokine release syndrome; CT = computed tomography; CTCAE = Common Technical Criteria for Adverse Events; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Co-operative Oncology Group; eCRF = electronic case report form; EoT = end of treatment; FDG PET = fluorodeoxyglucose positron emission tomography; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; CCI [redacted]; HTLV = human T lymphotropic virus; ICANS=Immune Effector Cell-Associated Neurotoxicity Syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; IgG = immunoglobulin G; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NT-proBNP = N-terminal pro B-type natriuretic peptide; PCR = polymerase chain reaction; PD = progressive disease; PK = pharmacokinetic; PMBC = peripheral blood mononuclear cell; Q3W = once every 3 weeks; Q6W = once every six weeks; Q9W = once every 9 weeks; Q12W = once every 12 weeks; RCL = replication competent lentivirus; RECIST = Response Evaluation Criteria In Solid Tumors; T4 = thyroxine; TSH = thyroid stimulating hormone; VSV-G = vesicular stomatitis virus G.

1. On Day 1, all samples will be collected and assessments performed prior to Lete-cel infusion (within 24 h), unless otherwise specified.
2. Week N visit for N>1 is scheduled on 1st day of the week; Day = 7N-6
3. Treatment fitness will be evaluated according to Section 5 and determined in consultation with Medical Monitor.
4. Medical history, including history of tobacco use, will be recorded in the eCRF at Screening and Baseline visits; however, any changes in medical history must be recorded in source documents throughout the conduct of the study
5. Neurological assessments are to be performed for patients with brain metastases and patients with neurological adverse events up to 12 weeks post resolution of the event. ICE should be measured on the day of Lete-cel infusion prior to treatment. Following infusion, ICE should be measured according to instructions in Section 10.9.8.2.
6. Includes all prescriptions, over-the-counter medications and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported. It also includes use of antibiotics and probiotics taken 60 days prior to lymphodepletion and up to Week 7 visit.
7. Includes temperature, blood pressure, pulse rate, respiratory rate, oxygen saturation and weight. Height will be collected at the Screening visit only.
8. Vital signs on day of Lete-cel 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. On pembrolizumab infusion days, vital signs should be taken pre- and post-infusion.
9. If participant's ECHO/MUGA at leukapheresis eligibility screening met eligibility for left ventricular ejection fraction ≥45% as specified in Section 5.1.2, and if prior ECHO/MUGA was obtained within 90 days prior to the first day of lymphodepletion, then a repeat ECHO/MUGA will not be required. Repeat ECHO/MUGA at baseline should be obtained 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 Section 10.9.5)

10. Collect a single ECG at baseline. If QTc is >480 msec, collect 2 more ECGs 5 minutes apart and use the average of those QT values to determine eligibility. If the average QTc is >480 msec, obtain a manual overread of the triplicate. Single ECGs will be collected at all other time points that require ECGs. ECG can also be performed at other time points if medically indicated. Participants with clinically significant cardiovascular risk factors (per Section 8.2.3) will undergo evaluation by a cardiologist prior to lymphodepletion.

11. Diagnostic quality CT scan of chest/abdomen/pelvis with contrast is required at Baseline (within 2 weeks prior to lymphodepletion), Week 7 (±7 days), Week 13 (±7 days), Week 19 (±7 days), Week 25 (±7 days), Week 34 (±7 days), and Q12W (±7 days) thereafter, until EoT. If a participant is found to have a tumor response by imaging, a follow-up confirmatory scan must be done no earlier than 4 weeks and no later than the next scheduled imaging time point after the initial scan showing response. If a participant is found to have progressive disease by imaging, a follow-up confirmatory scan must be done no earlier than 4 weeks and no later than 8 weeks after the initial scan showing PD. Investigator assessed RECIST v1.1[CCI] evaluation must be done following instructions in Appendix 10.

12. Any FDG PET/CT performed as part of clinical routine will be collected centrally but will not replace CT scans.

13. Brain MRI (or CT Scan if MRI not feasible) should be performed at Baseline (within 4 weeks prior to lymphodepletion) if more than 4 months have elapsed from last brain MRI. A repeat brain MRI prior to lymphodepletion would need to show stability or reduction of CNS metastases if any radiotherapy was administered after the MRI performed for leukopheresis eligibility screening. Brain MRI should be performed as clinically indicated thereafter (see Section 10.9.8).

14. Coagulation tests include INR, PTT or aPTT and fibrinogen. Coagulation tests should be taken at baseline, Day 1, 2, 3, 4, 5, 8 and 15.

15. 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 detailed in Table 4. Troponin and NT-proBNP / BNP tests should be monitored for participants with CRS Grade ≥2 as clinically indicated.

16. WOCBP must have a negative urine or serum pregnancy test (highly sensitive) at Baseline (within 24 hours prior to lymphodepletion), prior to Lete-cel infusion, and thereafter will need to have pregnancy tests performed at all visits indicated in the table for the duration of the contraception period (see Section 5.3.3.2 and Section 8.4.7).

17. 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.

18. Thyroid tests must be performed Q6W during pembrolizumab administration. See footnote 24 for first pembrolizumab administration.

19. See Table 11 for specifics on renal assessment.

20. Adverse events should be collected and reported as noted in Section 8.4.

21. PBMCs for Persistence will be collected at Baseline (Day -17 to Day - 9) and at Week 13, Week 25, and every 6 months thereafter (e.g., 12 months, 18 months, 24 months, etc.) until 5 years post Lete-cel infusion, then once a year for up to 15 years. After Week 22, the visit window for this assessment will be ±3 months. Some of these samples may be taken after the participant enters the LTFU protocol (GSK Study 208750) or study Part 5 (Table 8). PBMCs for Persistence may be collected in additional time points as clinically indicated. If vector persistence is undetected for two consecutive visit assessments and the participant is ≥2 years post-infusion, samples for persistence of gene modified cells will be discontinued.

22. PBMCs for RCL will be collected at Baseline (Day -17 to Day - 9) and at Week 13, Week 25, and every 6 months thereafter (e.g., 12 months, 18 months, 24 months, etc.) until 5 years post Lete-cel infusion, then once a year for up to 15 years. After Week 22, the visit window for this assessment will be ± 3 months. Some of these samples may be taken after the participant enters the LTFU protocol (GSK Study 208750). If vector persistence is undetected for two consecutive visit assessments and the participant is ≥2 years post-infusion, samples for RCL will be discontinued.

23. Participants will be hospitalized on the day of T-cell infusion (Day 1) and may be in the hospital for follow-up care until Day 3 as clinically indicated. Participants will be in close proximity to the hospital for at least 7 days post infusion. Additional hospitalization may be warranted based upon clinical need.

24. Arms B and C only. First pembrolizumab administration on Day 22 (Week 4 Day 1), then Q3W for up to 35 cycles. If toxicities that preclude pembrolizumab treatment, such as CRS Grade ≥2, are present at Day 22, the first infusion of pembrolizumab will be on Week 7 Day 1, in which case, Cycle 35 will occur on Week 109 Day 1. If AEs do not resolve by Week 7 Day 1 to ≤ Grade 1, pembrolizumab will not be administered, and the participant will be evaluated until disease progression or EoT. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.
25. For biomarker analysis, if genetic sample collection is not done at Baseline, it may be done at any other subsequent visit in the Interventional Phase. Collection of a genetic sample is optional and all participants must provide consent for sample collection and analysis prior to sampling.

CCI

[redacted]

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[redacted]

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[redacted]

Table 5 Schedule of Activities – Pembrolizumab Therapy Following Disease Progression after Lete-cel Infusion (Part 4-Arm A only)

Pembrolizumab (P) Week (W)	PBL	PW1	PW2	PW4	PW7	PW10 to PW103 (Q3W)
Visit Window[1]	-28 days[2]	±1 day	±3 days			±3 days
Pembrolizumab Eligibility[3]	X					
Physical Exam	X	X	X	X	X	X
Neurological Exam[4] and ICE	X	See note 4				
Prior/Concomitant Medications	X	X	X	X	X	X
ECOG	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
ECG[5]	X	X		X		
CT/MRI[6]	X				X[6]	X
RECIST Evaluation[6]	X				X	X
Hematology[9]	X	X	X	X	X	X
Chemistry[9]	X	X	X	X	X	X
Pregnancy Test[7]	X	See note 7				
CMV IgG and PCR[8]	See note 8					
TSH with Free T4[9]	See note 9					
CRP[10]		X	X	X	X	X
Ferritin[10]	See note 10					
Coagulation Tests[10]	See note 10					
Troponin and NT-proBNP/BNP[10]	See note 10					
Adverse Events		X	X	X	X	X
Vector Copies (Persistence for Safety) [blood]	See notes 11 and 12					
VSV-G DNA (RCL) [blood]	See notes 11 and 12					
Pembrolizumab administration		X		X	X	X

Notes

1. Week N visit for N>1 is scheduled on 1st day of the week; Day = 7N-6.
2. Baseline assessments required only if the assessments have not been performed within 28 days prior to first pembrolizumab administration.
3. See Section 5.1.4.
4. Neurological assessment for participants with brain metastases and those with neurological adverse events up to 12 weeks post resolution of the event.
5. Single ECG on the days of pembrolizumab administration, prior to infusion.
6. Pembrolizumab Baseline CT/MRI prior to pembrolizumab therapy must be obtained within 4 weeks prior to first pembrolizumab administration. If the CT/MRI has been obtained at PD within 4 weeks prior to pembrolizumab therapy initiation, this can be considered as baseline measurement. Diagnostic quality CT scan of chest/abdomen/pelvis with contrast is required every 6 weeks (±7 days) until PW25, at PW34, and then every 12 weeks (±7 days) thereafter, until EoT for pembrolizumab. If a participant is found to have a tumor response by imaging, a follow-up confirmatory scan must be done no earlier than 4 weeks and no later than the next scheduled imaging timepoint after the initial scan showing response. If a participant is found to have progressive disease by imaging, a follow-up confirmatory scan must be done no earlier than 4 weeks and no later than 8 weeks after the initial scan showing PD. Investigator assessed RECIST v1.1 CCI evaluation must be done following instructions in Appendix 10. Any FDG PET/CT performed as per clinical routine will be collected centrally but will not replace CT scans.
7. WOCBP will need to have pregnancy tests (highly sensitive) performed at all visits indicated in the table for the duration of the contraception period (see Section 5.3.3.2 and Section 8.4.7).
8. Only participants who are CMV IgG seropositive at PBL will continue to be monitored for CMV viremia by CMV DNA PCR post PBL.
9. Thyroid tests must be performed Q6W during pembrolizumab administration.
10. 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 detailed in Table 6. Troponin and NT-proBNP / BNP tests should be monitored for participants with CRS Grade ≥2 as clinically indicated.
11. PBMCs for Persistence and RCL testing will be collected at PW13, PW25, and every 6 months until EoT for pembrolizumab or disease progression, whichever comes first. Data collected at Baseline (Day -14 to Day - 9) prior to lete-cel will be used as baseline.
12. If vector persistence is undetected for two consecutive visit assessments and the participant is ≥2 years post-infusion, samples for RCL and persistence of gene modified cells will be discontinued. However, if VSV-G DNA copies are detected at any time point during year 1, refer to the safety monitoring procedures in Section 8.3.5.

See Table 6 for PK, Immunogenicity, and Biomarker Samples

EoT = end of treatment; FDG PET = fluorodeoxyglucose positron emission tomography; IgG = immunoglobulin G; MRI = magnetic resonance imaging; PBL = Pembrolizumab Baseline; PCR = polymerase chain reaction; PD = progressive disease; PK = pharmacokinetics; PW = Pembrolizumab Week; Q3W = once every 3 weeks; RCL = replication competent lentivirus; RECIST = Response Evaluation Criteria In Solid Tumors; VSV-G = vascular stomatitis virus G.

Note: Pembrolizumab therapy is only allowed in case of disease progression within the first 25 weeks after lete-cel infusion. Pembrolizumab therapy will not be allowed if disease progression occurs after the Week 25 scan. Pembrolizumab treatment will be administered for up to 35 cycles Q3W at 200 mg or until subsequent disease progression.

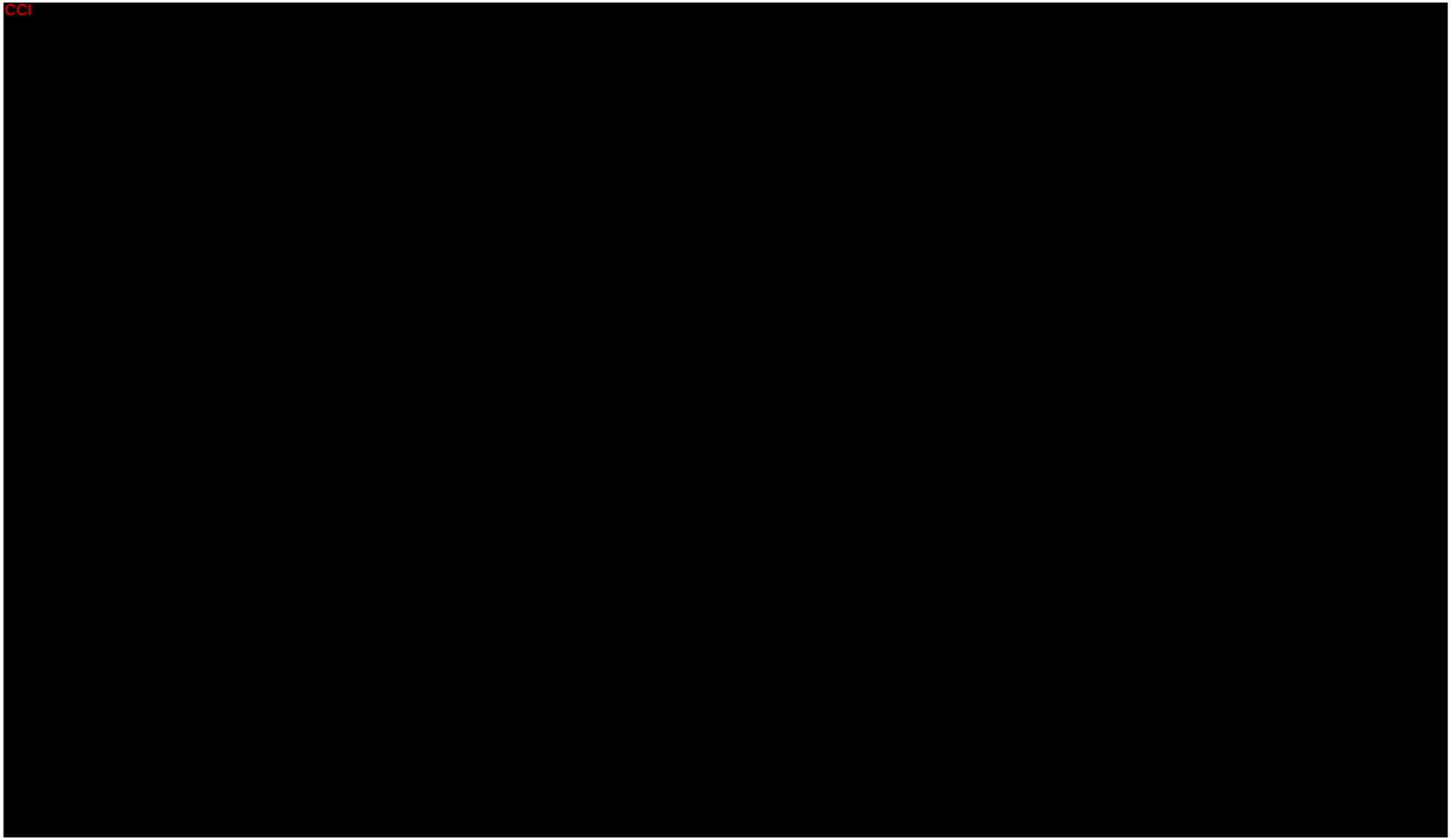
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Table 7 Schedule of Activities – End of Treatment/End of Interventional Phase

Day (D) / Week (W)	Completion/ Withdrawal[1]	Notes
Clinical Assessments and Procedures[2]		1. Participants will complete the EoT visit after completing interventional portion of the study (Parts 3 or 4; see Section 4.4.1), discontinuation of pembrolizumab (if relevant) or early withdrawal from the interventional phase. EoT visit is to be completed only once for each participant. All procedures and assessments, as indicated, should be performed preferably 4 weeks and no later than 60 days from last pembrolizumab treatment or visit, as relevant. If performed sooner, only complete assessments not already performed as part of last pembrolizumab treatment or visit. EoT visit must be completed prior to initiating non-protocol anti-cancer therapy, if relevant (See Section 6.9.1). 2. See Section 8 for details. 3. Includes all prescriptions, over-the-counter medications, and herbal remedies. Any use of mutagenic agents or investigational agents must also be reported. 4. Includes temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. 5. If clinically needed. 6. If a participant is found to have a tumor response or progressive disease by imaging via RECIST v1.1, 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 disease progression was first seen. A participant is not considered to have a response or progression until a follow-up scan confirms the finding. Any FDG PET/CT performed as per clinical routine will be collected centrally but will not replace CT scans. 7. If a CT / MRI assessment has been completed within the last 4 weeks, additional CT / MRI assessments are not required as part of EoT visit, unless it is confirmatory scan (within the schedule in Note #6, above). 8. If disease progression has been confirmed prior to EoT visit, additional CT / MRI assessments are not required as part of EoT visit. 9. Adverse events should be reported as noted in Section 8.4.
Prior/Concomitant Medications[3]	X	
Physical Exam	X	
ECOG	X	
Vital Signs / Height / Weight[4]	X	
ECG	X[5]	
CT / MRI[6,7,8]	X	
Hematology	X	
Chemistry	X	
Adverse Events[9]	X	
CCI [redacted]		
Correlative Studies and Research Assessments		11. Biopsies for research are taken at Baseline, Week 7, and at confirmation of PD, with the exception of participants for whom there is no safely accessible tumor tissue. 12. Liquid Biopsy samples should match tumor biopsy and/or CT/MRI assessment time points. See footnote 6 for CT/MRI assessment.
Tumor biopsy[11]	X	
Liquid Biopsy (blood)[12]	X	
Blood for Cell Phenotype and Functional Assays	X	
Cytokine Analyses	X	

Abbreviations: cfDNA = cell-free DNA; CT = computed tomography; CTCAE = Common Technical Criteria for Adverse Events; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Co-operative Oncology Group; EoT = end of treatment; FDG PET = fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; PD = Progressive Disease; W = Week.

Table 8 Schedule of Activities – Long Term Follow-up after Disease Progression or Completion of Interventional Phase (Part 5 or Study 208750)

Time post-infusion[1]													
	Year 1			**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Year 6-15[9]**	
Months	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**Annually**	**Unscheduled Visit[7]**
Visit Window	**±2 weeks**		**±3 months**									**±6 months**	
Medical History[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	X	X	X		
Subsequent anti-cancer therapies or allogeneic stem cell transplant (allo-SCT)[2,3]	X	X	X	X	X	X	X	X	X	X	X	X	
Delayed Adverse Events[4]	X	X	X	X	X	X	X	X	X	X	X	X[5]	
CBC with differential and Serum Chemistry[6]	X	X	X	X	X	X	X	X	X	X	X		
VSV-G DNA (RCL) and vector copies (Persistence) for safety (blood)[6,7]	X	X	X	X	X	X	X	X	X	X	X	X	
Survival Status[8]	X	X	X	X	X	X	X	X	X	X	X	X	X

Allo-SCT = allogeneic stem cell transplant; CBC = complete blood cell (count); RCL = replication competent lentivirus; VSV-G = vesicular stomatitis virus G

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. Collect new medical history/medications and chemotherapies and/or radiotherapy.
3. All participants who received pembrolizumab will be followed for 24 months after their last dose to ascertain if they are candidates to receive an allogeneic- stem cell transplant (allo-SCT). Participants who receive an allo-SCT within the 24-month follow-up period will be monitored for 18 months for post allo-SCT complications as described in Section 8.4.5.
4. Delayed adverse event collection is limited to:
   - New malignancies
   - New incidence or exacerbation of pre-existing neurologic disorder

- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of a hematologic disorder
- New incidence of infection (potentially related to gene modified cell therapy)
- Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy
- Specific events outlined in Section 8.3 for participants who received pembrolizumab and had allo-SCT

5. During years 6-15 of annual follow-up period, AEs and SAEs will be entered in the CRF if reported by the patient or investigator.
6. 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.
7. If vector persistence is undetected for two consecutive visit assessments and the participant is ≥2 years post-infusion, samples for RCL and persistence of gene modified cells will be discontinued.
8. If a participant is contacted between the scheduled visits, the date of last contact should be recorded as an unscheduled visit.
9. Subjects who do not have persistence of gene modified cells may be followed remotely during years 6-15.

2. INTRODUCTION

2.1. Study Rationale

Adoptive T-cell therapy (ACT) is a therapeutic approach that uses a patient's own T lymphocytes, obtained by leukapheresis, engineered to express a tumor-specific T-cell receptor (TCR), expanded *ex vivo*, and re-infused into the patient, with the aim of generating an anti-tumor T-cell immune response. The New York esophageal squamous cell carcinoma 1 (NY-ESO-1) and cancer testis antigen 2 (LAGE-1a) antigens are tumor-associated proteins that have been found in several tumor types, including non-small cell lung cancer (NSCLC). Previous clinical trials using ACT with T-cells directed against NY-ESO-1/LAGE-1a have shown objective responses between 40% to 60% in participants with synovial sarcoma, metastatic melanoma, and multiple myeloma [Robbins, 2011; Robbins, 2015; Rapoport, 2015].

Pembrolizumab (KEYTRUDA) is a monoclonal antibody that acts specifically on tumor-targeting T-cells to block the interaction of programmed death protein 1 (PD-1) and its ligand (PD-L1) interaction and increase the anti-tumor function of T-cells. In this study, pembrolizumab will be used in combination with NY-ESO-1/LAGE-1a TCR engineered patient T-cells (lete-cel) to potentially further improve the therapeutic effect.

2.2. Background

Lung cancer is the most common cause of cancer death, accounting for 1.69 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 advanced-stage metastatic NSCLC that is determined positive for a specific molecular alteration (such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), and BRAF), targeted single-agent approaches are recommended [NCCN, 2017; Postmus, 2017]. For metastatic non-squamous NSCLC who present with either wild-type (WT) or Kirsten rat sarcoma viral oncogene (KRAS) mutated tumors, the incorporation of an anti-PD-1 inhibitor, such as, pembrolizumab, to the pemetrexed/carboplatin backbone is an option for some patients as first-line treatment through the recent accelerated approval of this triplet combination by the Food and Drug Administration (FDA) [Langer, 2016]. An alternative current standard for NSCLC is pembrolizumab as a single-agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] ≥50%) or, in subsequent lines of therapy as a single-agent for the treatment of metastatic NSCLC expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy [Reck, 2016]. Additional subsequent-line treatment options include other single-agent anti-PD-1/PD-L1 inhibitors (for example, nivolumab, atezolizumab) if not administered in the first line

[Brahmer, 2015; Rittmeyer, 2017]. 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]. Thus, patients with NSCLC that has failed anti-PD-1/PD-L1 blockers (alone or in combination with chemotherapy) have a high unmet medical need for treatment advances that improve progression-free survival (PFS) and overall survival (OS).

2.2.1. Lete-cel

Lete-cel consists of autologous T cells transduced with lentiviral vectors to express the affinity enhanced TCR (c259) and is being investigated in multiple GSK sponsored pilot clinical trials in participants with metastatic synovial sarcoma, advanced myxoid/round cell liposarcoma, and/or relapsed refractory multiple myeloma who are HLA-A*02^{+} and whose tumors express NY-ESO-1 and/or LAGE-1a. NY-ESO-1 and LAGE-1a are members of the cancer-testis family of tumor associated antigens. Published data indicate that 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 a frequency of expression of NY-ESO-1 of 12% in lung adenocarcinoma and 26% in squamous cell carcinoma and a frequency of expression of LAGE-1a in 8.5% of adenocarcinoma and 21% of squamous cell carcinoma. An HLA-A2 binding peptide (SLLMWITQC), corresponding to amino acids 157 to 165 in both NY-ESO-1 and LAGE-1a, that can be recognized by NY-ESO-1 reactive T-cells has been identified. Lete-cel is a product of genetically engineered T-cells with an enhanced affinity T-cell receptor toward the SLLMWITQC peptide bound to HLA-A*02.

Most clinical protocols with TCR gene therapy have incorporated conditioning of the patient with a lymphodepleting chemotherapy regimen prior to T-cell infusion [Rohaan, 2019]. As of 15 May 2018, 3 participants with NSCLC have received lete-cel in combination with lymphodepleting chemotherapy (Section 6.3) in an ongoing trial (Study 208749). The incorporation of lymphodepletion prior to ACT may enhance immune reconstitution by the transferred cells and increase tumor-specific responses. Immune reconstitution is enhanced through homeostatic mechanisms that facilitate expansion of T lymphocytes [Baccala, 2005], facilitate trafficking of the engineered T-cells [Pinthus, 2004] and also improve the persistence of infused T-cells. Lymphodepletion can also enhance the activity of the adoptively transferred cells via the removal of inhibitory factors such as regulatory T-cells [Wolf, 2003] and can activate antigen presenting cells through the induction of inflammatory cytokines and induction of tumor apoptosis with resulting cross presentation of tumor antigens to T-cells.

2.2.2. Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed death protein 2 ligand (PD-L2). Based on *in vitro*

preclinical data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab is indicated for the treatment of patients across a number of indications. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for other advanced malignancies.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

2.2.2.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and a favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and a high ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, 2005; Hunder, 2008].

The PD-1 receptor-ligand interaction is a major pathway that is hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, 2005; Okazaki, 2001].

The structure of murine PD-1 has been resolved [Zhang, 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an immunoglobulin variable–type (IgV) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, Src homology 2 containing phosphatases 1 and 2 (SHP-1 and SHP-2), to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, 2001; Chemnitz, 2004; Sheppard, 2004; Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [Parry, 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in NSCLC.

2.2.2.2. Pre-clinical Data

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [Hirano, 2005; Blank, 2004; Weber, 2010; Strome, 2003; Spranger, 2014; Pilon, 2010]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [Strome, 2003; Curran, 2010; Pilon, 2010; Nomi, 2007; Zhang, 2004]. In such studies, tumor infiltration by CD8+ T-cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T-cell function *in vivo* [Curran, 2010]. Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (Refer to pembrolizumab IB/approved labeling).

2.2.3. Rationale for the Combination Regimen

The immunomodulatory molecule PD-L1 is expressed on both tumor cells and immune cells within the tumor microenvironment. Furthermore, the expression of PD-1 is upregulated on activated T-cells. The expression of immunosuppressive receptors such as PD-1 is one mechanism by which the efficacy of ACT could be inhibited. In a xenograft model of NSCLC, it was observed that PD-1 expression was significantly upregulated on NY-ESO-1 specific T-cells following infiltration into the tumor. *In vivo* synergy was observed between NY-ESO-1 specific T-cells and anti PD-1, resulting in significantly enhanced control of tumor growth over NY-ESO-1-specific T-cells alone [Moon, 2016]. Therefore, the combination of lete-cel and pembrolizumab could result in a synergistic effect due to the inhibition of PD-1 on lete-cel. This combination is currently under clinical investigation for the treatment of multiple myeloma (NCT03168438 [ADP-0011-004]).

Thus, patients with NSCLC that has failed PD-1/PD-L1 checkpoint blockade therapy (alone or in combination with chemotherapy), as well as patients with NSCLC that has relapsed following standard of care (SoC) tyrosine kinase inhibitors (TKIs), have a high unmet medical need for treatment advances to improve PFS and OS.

2.3. Benefit/Risk Assessment

The results of clinical and non-clinical studies of lete-cel are summarized in the IB (GlaxoSmithKline Document Number RPS-CLIN-015027). Likewise, the results of pembrolizumab studies are summarized in the KEYTRUDA prescribing information. It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation, as these studies are designed to provide information about the safety and effectiveness of investigational medicines. The potential benefits, risks and risk mitigation strategy for this study are outlined in this section. The goal of the risk management measures is to maximize the chance of therapeutic benefit while mitigating and better understanding the risks of treatment with lete-cel alone or in combination with pembrolizumab.

2.3.1. Risk Assessment

Table 9 Summary of Risks and Risk-Mitigation Strategies Related to Study Treatments

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Lymphodepleting Chemotherapy (Fludarabine/Cyclophosphamide)		
• Myelosuppression • Immunosuppression • Bone marrow failure and infection • Cardiotoxicity • Pulmonary toxicity • Urinary tract and renal toxicity • Veno-occlusive disease • Secondary malignancy • Hyponatremia • Neurotoxicity	Cases were reported with both drugs.	Please refer to the prescribing information of fludarabine and cyclophosphamide and Appendix 9 (Section 10.9.9)
• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Decreased vision • Peripheral neuropathy	Cases were reported with fludarabine	Please refer to the prescribing information of fludarabine.
Lete-cel		
Cardiac arrest	Potential risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been 2 reports of unexpected fatal cardiac arrest. The first occurred 5 months after T-cell infusion and was confounded by hypotension due to poor oral intake and concurrent renal insufficiency. The second occurred approximately 1 week after T-cell infusion in the setting of a recent fungal catheter line infection, concurrent treatment with caspofungin and multifocal pneumonia / edema seen on chest CT.	Participants with significant cardiac risk factors or with CRS ≥Grade 2 will receive close cardiac monitoring (Section 8.2.3 and Section 10.9.5). 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 (Section 8.2.4). Central lines should be closely monitored for infection (Section 10.9.2). Systemic fungal infections are excluded (Exclusion criterion #8) Monitoring of risk of increased cardiac toxicity with the use of anti-microbials (Section 10.9.2.6)
Cytokine Release Syndrome (CRS)	Identified risk due to TCR T-cell infusion, considered an adverse event of special interest (AESI)	Participants with pre-existing autoimmune disorders are excluded (Section 5.1 and Section 5.2). See management for CRS, Appendix 9 (Section 10.9.5). Events ≥ Grade 3 must be reported as SAEs and submitted to GSK within 24 hours.

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Pneumonitis	Potential risk associated with TCR T-cell infusion, considered an AESI	I/E criteria exclude participants with pre-existing autoimmune disorders (Section 5.2.1). See Appendix 9 for Supportive Care Guidance.
Graft-versus-Host disease (GVHD)	Identified risk associated with TCR T-cells reacting against normal tissues and organs, considered an AESI	Participants with pre-existing autoimmune disorders are excluded (Section 5.1 and Section 5.2). See management for GVHD, Appendix 9 (Section 10.9.6)
Haematopoietic cytopenias (including Pancytopenia with bone marrow failure/aplastic anemia)	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion, considered an AESI	Participants with cytopenias are excluded. See management for pancytopenia, Appendix 9 (Section 10.9.7)
Haemorrhage secondary to thrombocytopenia	Identified risk associated with lymphodepletion chemotherapy and TCR T-cell infusion. There have been reports of haemorrhage (including intracranial and pulmonary) in participants with severe, prolonged thrombocytopenia	Protocol guidance on Blood product support provides recommendation on platelets levels to be maintained in the in-patient setting and the out-patient setting, as per Section 10.9.3
Hypersensitivity	Identified risk due to lete-cel infusion. Hypersensitivity reactions (including anaphylaxis) may be due to the 5% (v/v) DMSO in lete-cel.	Participants with history of allergic reactions to any agents used in the study are excluded. See Section 5.2.2 for details. Participants will be premedicated against potential infusion reactions with antihistamines on the day of lete-cel infusion. See Section 6.4.1 for details.

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
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 5.2 for details. Lymphodepletion dose will be modified in participants with potentially reduced bone marrow reserve. See Section 6.3.1 for details. Participants with active infection are excluded. Participants with CMV seropositivity will be monitored regularly for viral reactivation. For herpes simplex virus and varicella zoster virus prophylaxis, participants will receive acyclovir or valacyclovir for one year from LD. Prophylaxis will be given to those with HBV seropositivity. See Section 5.2 and Section 10.9.2 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 5.1.2). Investigator must discuss with Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in participants at risk (Section 6.3.1). G-CSF to be administered in accordance with ASCO guidelines or institutional practice (Section 6.3 and Section 10.9). Dose modifications for fludarabine and cyclophosphamide (Section 6.3) Grade 4 Neutropenia events lasting ≥28 days must be submitted to GSK within 24 hours (Section 8.4.4).
Decreased Vision	Potential risk: There was a report of decreased vision in a patient who received lete-cel following lymphodepletion with fludarabine and cyclophosphamide.	Dose reductions for fludarabine for renal impairment. Investigator must discuss with Medical Monitor or designee to determine the need for dose modification of the lymphodepletion regimen in patients at risk (Section 6.3)

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Guillain-Barré Syndrome (GBS)/Acute inflammatory demyelinating polyneuropathy	Potential risk associated with TCR T-cell infusion. Two participants who received lete-cel developed GBS.	Participants with prior or active demyelinating disease will be excluded (Section 5). Neurologic consultation is required for patients with Grade 2 or higher neurologic events of a ≥7-day duration. Any potential future recurrence of GBS will lead to a pause in study enrollment until further investigation.
Treatment-related inflammatory response at tumor site(s)	Potential risk associated with TCR T-cell infusion	Routine monitoring and testing as clinically required.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Potential risk associated with inflammation in the brain following TCR T-cell infusion. There have been reports of ICANS in participants who received lete-cel.	Participants with brain metastases with features associated with increased risk of ICANS are excluded (Section 5.1.3). Monitoring criteria for ICANS are described in Section 10.9.8.and Table 15, respectively.
Insertional oncogenesis	Potential risk in T-cells transduced with lentiviral vector	Routine pharmacovigilance (PV). To be monitored in the LTFU Protocol (GSK Study 208750) or LTFU portion of this study (Part 5). Monitoring to follow the recommendations set forth in the FDA guidance [FDA, 2020a]. PBMC samples are used as a surrogate sample for monitoring insertional oncogenesis by polymerase chain reaction (PCR) for gene modified cells in the blood.
Replication competent lentivirus (RCL)	Potential risk associated with use of lentivirus	Routine PV. To be monitored in the LTFU Protocol (GSK Study 208750) or LTFU portion of this study (Part 5). Samples will be tested for the presence of VSV-G DNA copies (Section 8.3.5)
On/Off-Target Off-Tumor Risks	Potential risk associated with use of lentivirus	To be monitored in the LTFU Protocol (GSK Study 208750) or LTFU portion of this study (Part 5). Protocol includes eligibility criteria (Section 5.1 and Section 5.2), routine PV (Section 8.3), and management strategies as appropriate to limit, diagnose, characterize and treat toxicities related to potential risks (Appendix 9).
Pembrolizumab		
Immune related reactions • Pneumonitis • Colitis • Nephritis • Neuritis • Hepatitis	Identified risks caused by an excessive T-cell immune activation and potential expansion and activation of T-cell clones against normal tissues	Please refer to Appendix 9, Section 10.9.

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
• Skin inflammation • Endocrinopathies		
Infusion reaction (pembrolizumab)	Identified risk associated with pembrolizumab infusion	Please refer to the KEYTRUDA prescribing information.
Interaction with lete-cel	Theoretical risk that anti-PD-1 treatment with pembrolizumab could exacerbate or trigger potential lete-cel and pembrolizumab-related side effects listed above.	The participants treated with the combination regimen of lete-cel and pembrolizumab will be carefully monitored through frequent visits and AE monitoring (Appendix 9 and Table 15)
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.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CRS = cytokine release syndrome; DSUR = development safety update report; FDA = Food and Drug Administration; GBS = Guillain-Barré Syndrome; GSK = GlaxoSmithKline (Sponsor); GVHD = graft versus host disease; I/E = inclusion/exclusion; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; KEYTRUDA = pembrolizumab; LTFU = long-term follow-up; PD-1 = programmed death protein 1; PV = pharmacovigilance; RCL = replication competent lentivirus; SAE = serious adverse event; TCR = T-cell receptor; VSV-G = Vesicular Stomatitis Virus G.

Risk Assessment for Lete-cel

The known safety profile of lete-cel is based on 166 participants who have undergone leukapheresis, of which 125 have been treated as of 27 January 2021 (GSK Document Number RPS-CLIN-015027).

In the integrated sponsored trials, 125 subjects have received both lymphodepletion and lete-cel; sixteen (16) of these subjects [11 subjects with synovial sarcoma, 4 subjects with multiple myeloma, and 1 with NSCLC] have received a second infusion of lete-cel after progressive disease following response (or prolonged stable disease) to their initial infusion.

Treatment-emergent adverse events (TEAEs) which occurred in ≥50% of subjects following lete-cel infusion were leukopenia/white blood cell (WBC) decreased (81%), neutropenia/neutrophil count decreased (80%), nausea (78%), anemia/ red blood cell (RBC) decreased (78%), thrombocytopenia/platelet count decreased (77%), fatigue (70%), pyrexia (66%), diarrhea (57%), and lymphopenia/lymphocyte count decreased (54%). Overall, there were no apparent significant differences in reported TEAEs between subjects receiving 1 or 2 infusions.

Treatment-emergent serious adverse events (SAEs) occurred in 74 (59%) subjects across all studies. Treatment-emergent SAEs occurring in 2 or more subjects following lete-cel cell infusion were cytokine release syndrome (CRS) (15%); febrile neutropenia and pyrexia (11%); neutropenia/neutrophil count decreased (10%);

thrombocytopenia/platelet count decreased (6%); dyspnea and rash/rash maculo-papular (5%); hypotension (4%); dehydration, diarrhea, and pleural effusion (3%); and acute kidney injury, anemia/RBC decreased, atrial fibrillation, hypoxia, nausea, pancytopenia, pneumonia, bone marrow failure, chills, cough, Guillain-Barré syndrome, hemoptysis, leukopenia/WBC decreased, pneumonitis, pulmonary hemorrhage, Staphylococcal infection, tumor pain, unspecified graft-versus host disease (GVHD) - other (lung, bone marrow, not specified), and vomiting (2%). The SAE profile following a second infusion of lete-cel was consistent with that experienced for all subjects infused.

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

- one subject with synovial sarcoma died due to the treatment-related SAE of bone marrow failure on Day 96, despite supportive care for pancytopenia with febrile neutropenia and bacteremia (blood cultures tested positive for Pseudomonas aeruginosa on Day 59 and for cytomegalovirus on Day 69; infections were ongoing at time of death);
- one subject with MRCLS was reported to die due to the treatment-related SAE of cardiac arrest on Day 161. This subject had a Grade 3 cytokine release syndrome (CRS) complicated by supraventricular tachycardia and hypotension related to therapy immediately following infusion. He also had an anterior chest wall mass detected at baseline; contribution of this mass to the cardiac complications is unclear. GSK's assessment of this report indicates that the exact cause of death remains unclear, but not likely related to the study treatment;
- one subject with ovarian cancer died on Day 138 due to disease progression unrelated to treatment, which was reported as an SAE;
- one subject with synovial sarcoma was reported as having died on Day 58 due to Grade 5 hemoptysis unrelated to study treatment and which was reported as an SAE before the data cut-off for GSK3377794 IB, 2021 (GSK Document Number RPS-CLIN-015027). Following the data cut-off for the IB update and after autopsy report the site clarified that the primary cause of death was disease progression; hemoptysis was a concomitant event.

There were no fatal SAEs reported among subjects who received a second infusion of lete-cel.

Refer to the most recent Investigator's Brochure (IB) for lete-cel for detailed information.

Risk Assessment for Pembrolizumab

Pembrolizumab monotherapy was discontinued due to adverse reactions in 8% of 682 participants with metastatic NSCLC in the KEYNOTE-010 trial (a Phase 3 randomized controlled clinical trial with pembrolizumab versus docetaxel in previously treated, PD-L1-positive, advanced NSCLC [Herbst, 2016] (NCT01905657). The most common AE resulting in permanent discontinuation of pembrolizumab was pneumonitis (1.8%). Adverse reactions leading to treatment interruption occurred in 23% of participants; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). The most common AEs (occurring in at least 20% of participants and at a higher incidence than with

docetaxel) were decreased appetite (25% vs 23%), dyspnea (23% vs 20%), and nausea (20% vs 18%).

See Section 6.10.2 for pembrolizumab dose modification guidelines.

Risk Assessment for the Lete-cel Plus Pembrolizumab Combination

The combination of lete-cel and pembrolizumab is currently being tested in participants with multiple myeloma [NCT03168438]. The current NSCLC study is the first time that a single-dose of lete-cel will be given to participants prior to pembrolizumab treatment. The theoretical risk is that anti-PD-1 treatment with pembrolizumab could exacerbate or trigger potential lete-cel-related side effects listed above. To mitigate this risk, participants treated with the combination regimen of lete-cel and pembrolizumab will be carefully monitored through frequent visits and for AEs.

2.3.2. Benefit Assessment

2.3.2.1. Benefit for Lete-cel

The TCR approach to engineered T-cell therapy is attractive because TCRs can recognize not only cell surface proteins (as is the case with chimeric antigen receptor T-cells [CAR-T]) but also any internal protein, since TCRs recognize peptide fragments in the context of HLA. In addition, the TCR approach mimics the natural function of the T-cell by recruiting the endogenous signaling molecules and adhering to correct spatial orientation between the T-cell and its target. These aspects may contribute to enhanced safety and activity of TCR engineered cells.

As of 27 January 2020, 103 participants have been treated with lete-cel (engineered using a lentiviral vector) in 5 clinical trials in the indications of multiple myeloma, synovial sarcoma, myxoid/round cell liposarcoma, melanoma, and ovarian cancer. Objective responses have been observed in the on-going synovial sarcoma study, 208466 (formerly ADP-04511, and in the myeloma (transplant) study, 209393 (formerly ADP-01411 [GSK Document Number RPS-CLIN-015027]. Additionally, 38 participants were treated in an Investigator sponsored study conducted by the National Cancer Institute (NCI) [Robbins, 2008; Zhao, 2007], where the T-cells were modified using a retroviral vector, expanded using NCI cell processing methods and administered in conjunction with IL-2. HLA-A2 participants with melanoma and synovial sarcoma tumors expressing NY-ESO-1 were recruited. Eleven of 18 participants (61%) with synovial sarcoma and 11 of 20 participants (55%) with multiple myeloma demonstrated objective clinical responses. The estimated overall 3- and 5-year survival rates for participants with synovial cell sarcoma were 38% and 14% respectively, while the corresponding estimated survival rates for participants with melanoma were both 33% [Robbins, 2015]. In addition, 2 participants with gastroesophageal cancer have been treated in the ATTACK-OG clinical trial.

Thus, there is good evidence to support the potential therapeutic benefit of lete-cel in participants with advanced or metastatic NSCLC. Refer to the most recent Investigator's Brochure (IB) for lete-cel for detailed background information.

2.3.2.2. Benefit for Pembrolizumab

Pembrolizumab has shown to prolong OS and have a favorable benefit-risk profile in patients with previously treated, PD-L1-positive, advanced NSCLC. The Keynote-010 trial enrolled 1034 participants with previously treated NSCLC with PD-L1 expression on at least 1% of tumor cells. In the total population, the median OS was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel. The OS was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (HR 0.71, 95% CI 0.58–0.88; p=0.0008) and for pembrolizumab 10 mg/kg versus docetaxel (0.61, 0.49–0.75; p<0.0001). The median PFS was 3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel (0.88, 0.74–1.05; p=0.07) or for pembrolizumab 10 mg/kg versus docetaxel (HR 0.79, 95% CI 0.66–0.94; p=0.004). Grade 3 to 5 treatment-related AEs were less common with pembrolizumab than with docetaxel (13% with 2 mg/kg, 16% with 10 mg/kg, and 35% with docetaxel).

2.3.2.3. Benefit for the Combination Regimen

There is evidence of clinical benefit from each of the individual agents in multiple tumor types to support the investigation of the potential augmented activity of lete-cel in combination with pembrolizumab in advanced or recurrent NSCLC (see Study Rationale, Section 2.1).

2.3.3. Overall Benefit - Risk Conclusion

Patients with advanced or metastatic NSCLC positive for NY-ESO-1 and LAGE-1a who have progressed following other therapies constitute a population with a high unmet medical need. Data from preclinical studies support the efficacy, specificity, and safety of lete-cel. Clinical data from participants summarized in the Investigator Brochure and the NCI and UPENN studies [Robbins, 2015; Rapoport, 2015; GSK Document Number RPS-CLIN-015027] demonstrate the safety and activity of lete-cel sufficiently to warrant further clinical investigation in participants with NSCLC.

Based on the known clinical activity of pembrolizumab in patients with NSCLC, the addition of lete-cel to pembrolizumab in participants with tumors positive for NY-ESO-1 and LAGE-1a may further improve clinical benefit.

3. OBJECTIVES AND ENDPOINTS

Table 10 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of autologous genetically modified T-cells (lete-cel) in human leukocyte antigen (HLA) HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive participants with NY-ESO-1 and/or LAGE1a-positive advanced NSCLC alone [Arm A] or lete-cel in combination with pembrolizumab in participants with NSCLC lacking actionable genetic aberrations [Arm B] and participants with NSCLC with an actionable genetic aberration [Arm C]	• Frequency and severity of AEs, serious adverse events (SAEs) and AEs of special interest (AESIs; as defined in protocol) • AE/SAEs leading to dose delays and/or withdrawals in participants who received lete-cel alone or in combination with pembrolizumab
• To determine the response to lete-cel alone [Arm A] or lete-cel in combination with pembrolizumab in participants with NSCLC lacking actionable genetic aberrations [Arm B] and participants with NSCLC with actionable genetic aberrations [Arm C]	• Overall Response Rate (ORR) (investigator assessed according to RECIST v1.1)
Secondary - Efficacy	
• To further investigate the anti-tumor activity of lete-cel alone or lete-cel in combination with pembrolizumab according to RECIST v1.1 criteria	• Progression-Free Survival (PFS) • Disease Control Rate (DCR) • Duration of Response (DoR) • Time to Response (TTR)
Secondary - Pharmacokinetics	
• To characterize in vivo cellular PK profile (levels, expansion, persistence) of NY-ESO-1 specific (c259) T cells	• Maximum transgene expansion (Cmax) • Time to Cmax (Tmax) • Area under the time curve from zero to

CCI [redacted]

Objectives	Endpoints
CCI	

Abbreviations:
CCI AE = adverse event/s; AESI = adverse event of special interest; AUC(0-t) = area under the time curve from zero to time t; Cmax = maximum persistence; CRS = cytokine release syndrome; DCR = disease control rate; DoR = duration of response (iDoR = DoR based on CCI); ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; FDG = fluorodeoxyglucose; G-CSF = granulocyte colony stimulating factor; HLA = human leukocyte antigen; IL = interleukin; CCI LAGE-1a = cancer testis antigen 2; NSCLC = non-small cell lung cancer; NY-ESO-1 = New York esophageal squamous cell carcinoma 1; ORR = overall response rate (iORR = ORR based on CCI); CCI CCI PD-L1 = programmed death protein 1 ligand; PET = positron emission tomography; PFS = progression-free survival CCI PRO-CTCAE = Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria In Solid Tumors CCI); CCI ; SAE = serious adverse event; TCR = T-cell receptor; CCI Tmax = time to Cmax; CCI ; TTR = time to response; WT = wild-type.

4. STUDY DESIGN

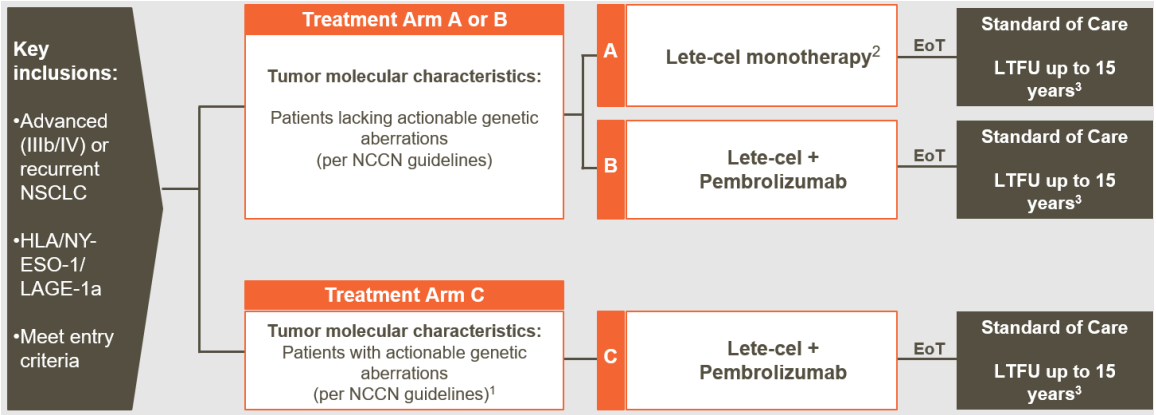
4.1. Overall Design

This is a multi-arm, open-label study of lete-cel in HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive adults whose tumors express NY-ESO-1 and/or LAGE-1a. The ability to achieve objective responses in diverse tumor types supports a hypothesis that HLA and antigen expression are biomarkers that identify a population of participants who may benefit from lete-cel.

This study will enroll participants who have unresectable Stage IIIb or Stage IV NSCLC and also fit study eligibility criteria (See Section 5).

The study will consist of 3 arms – Arms A, B, and C (Figure 2):

Figure 2 Study Schema



Abbreviations: EoT = end of treatment; HLA = human leukocyte antigen; LAGE-1a = cancer testis antigen 2; NCCN = National Comprehensive Cancer Network; NSCLC = non-small cell lung cancer; NY-ESO-1 = New York esophageal squamous cell carcinoma 1; PD-1 = programmed death protein 1; PD-L1 = PD-1 ligand; LTFU = long--term follow--up.

1. NSCLC patients with actionable genetic aberrations may receive treatment as part of Arm C only following treatment with targeted standard of care therapy (NCCN or equivalent country-guidelines (e.g., ESMO, NICE, etc.), as applicable).
2. Option of pembrolizumab therapy at time of disease progression following lete-cel administration and based on benefit-risk evaluation with Sponsor's Medical Monitor (or designee) approval.
3. LTFU requires participant enrollment in a dedicated LTFU protocol (GSK Study 208750). If not yet enrolled in the LTFU protocol, participants will be followed per LTFU schedule under this protocol (Part 5) until enrolled in the separate LTFU protocol (see Table 8).

The investigational treatment is intended for patients with NSCLC lacking actionable genetic aberrations that has failed PD-1/PD-L1 checkpoint blockade therapy (Arms A or B) or patients with NSCLC with actionable genetic aberrations (e.g., BRAF, ALK/ROS1, etc.) that has failed SoC targeted therapies as per NCCN or equivalent country-guidelines (e.g., ESMO, NICE, etc.), as applicable (Arm C).

Arms A and B:

Participants with NSCLC lacking actionable genetic aberrations will be assigned to receive either lete-cel monotherapy single infusion (Arm A) or receive a single IV infusion of lete-cel on Day 1 followed by pembrolizumab to be initiated on Day 22 (Week 4 Day 1) and continued for up to 35 cycles, or until disease progression, or intolerable toxicity, whichever occurs first (Arm B). There will be no re-treatment with lete-cel in this study.

In Arm A, participants who progress within 25 weeks following lete-cel infusion may be offered anti-PD-1 therapy with pembrolizumab following benefit-risk evaluation and approval by the Sponsor's Medical Monitor (or designee). Pembrolizumab treatment will be administered for up to 35 cycles or until subsequent disease progression or intolerable toxicity. Pembrolizumab therapy will not be allowed if disease progression occurs after the 25-week scan.

Assignment of participants to Arm A or B will be determined by the Sponsor. Participants will be assigned to Arm A first and then to Arm B.

Enrollment will aim to include approximately 5 squamous cell carcinoma (SCC) NSCLC participants lacking actionable genetic aberrations.

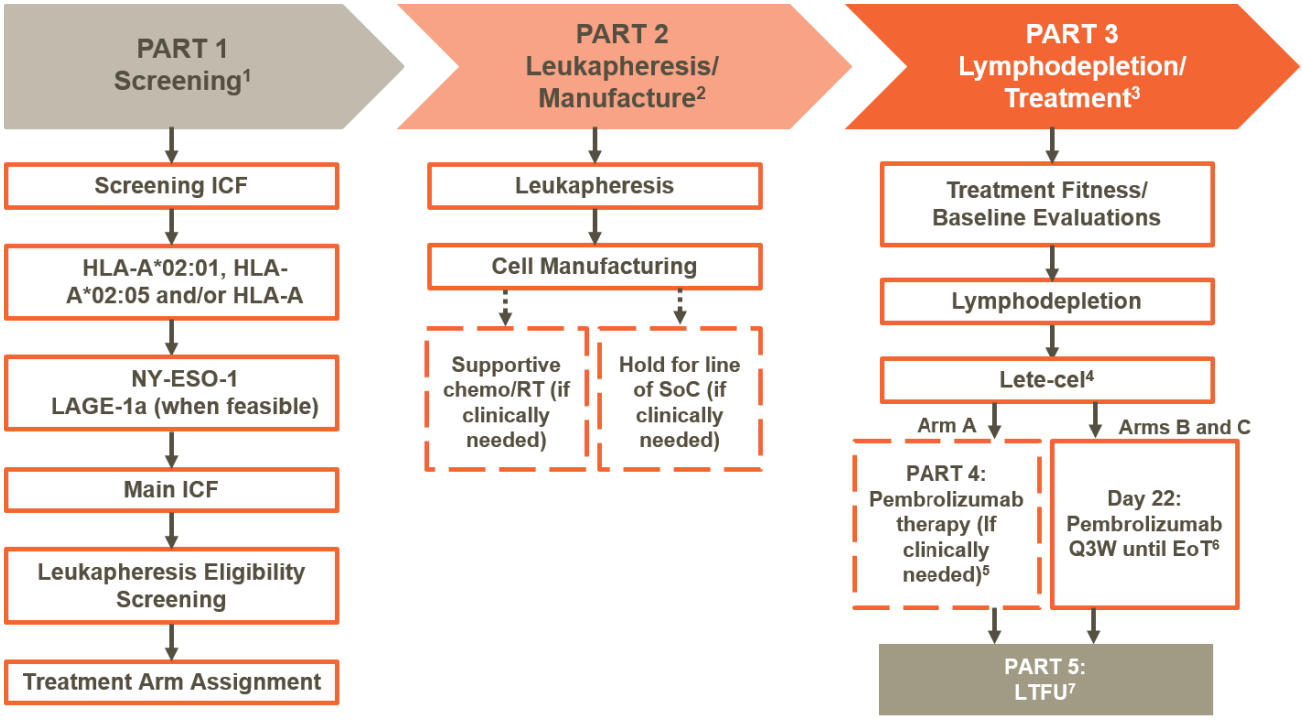
Arm C:

Participants with NSCLC with actionable genetic aberrations will be assigned to Arm C and receive the same treatment as participants in Arm B. There will be no re-treatment with lete-cel in this study.

Participant Flow

Figure 3 summarizes the participant flow in the study.

Figure 3 Participant Flow



Abbreviations: CRS = cytokine release syndrome; EoT = end of treatment; HLA = human leukocyte antigen; ICF = informed consent form; I/E = inclusion/exclusion; LAGE-1a = cancer testis antigen 2; NSCLC = non-small cell lung cancer; NY-ESO-1 = New York esophageal squamous cell carcinoma 1; PD = progressive disease; Q3W = once every 3 weeks; RT = radiotherapy; SoC = standard of care.

1. Screening may start at any time after diagnosis of advanced Stage IIIb or IV or recurrent NSCLC.
2. Leukapheresis may start once the eligibility criteria are fulfilled. Wash-out times as indicated in Table 12 may apply.
3. Lymphodepletion starts at clinical and / or radiographic disease progression. Wash-out times as indicated in Table 12 may apply.
4. Participants will receive a single dose of lete-cel five (5) days after completing the lymphodepleting chemotherapy (this is considered Day 1).
5. Participants in Arm A who have PD following treatment with lete-cel at or before the scheduled Week 25 scan may be offered pembrolizumab therapy (Part 4) following assessment of eligibility for pembrolizumab treatment, benefit-risk evaluation, and approval by the Sponsor's Medical Monitor (or designee). (see Section 6.4.4).
6. In Arms B and C, the first pembrolizumab administration is on Day 22 (Week 4 Day 1). If toxicities that preclude pembrolizumab treatment, including such as CRS Grade ≥2, are present at Day 22, infusion of pembrolizumab will start on Week 7 Day 1. In either case, pembrolizumab will then be administered Q3W up to 35 cycles or PD as described in Section 6.5.
7. LTFU requires participant enrollment in a dedicated LTFU protocol (GSK Study 208750). If not yet enrolled in the LTFU protocol, participants will be followed per LTFU schedule under this protocol (Part 5) until enrolled in the LTFU protocol (see Table 8).

Note: Dashed boxes and arrows indicate activities that may be performed based on clinical need.

The study consists of 5 parts:

Part 1 (Screening)

Part 2 (Leukapheresis)

Part 3 (Interventional Phase: Lymphodepletion/Treatment)

Part 4 (Pembrolizumab Therapy Following Disease Progression after Lete-cel Infusion, for Arm A ONLY)

Part 5 (Long-Term Follow-Up)

4.1.1. Part 1: Screening

Part 1 (Screening) will consist of 2 phases: target expression screening and leukapheresis eligibility screening.

Target Expression Screening

Target expression screening may proceed once informed consent has been obtained and patient is deemed eligible based on inclusion / exclusion criteria for target expression screening, as listed in Section 5.

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, when feasible, LAGE-1a expression will also be evaluated on tumor tissue from a formalin-fixed and paraffin-embedded (FFPE) archival (most recent preferred) or fresh biopsy (see Section 8.9.2 for more details). Please refer to Study Reference Manual for additional information on target expression screening procedures.

Participants screened or enrolled in other GSK studies may be considered for enrollment to this study, where it is IRB/IEC approved, on a case-by-case scenario following risk/benefit evaluation between the Investigator and Sponsor Medical Monitor (or designee). See Section 4.1.1.1 for details.

Leukapheresis Eligibility Screening

Once participants are deemed positive for HLA and tumor antigen expression, they will sign the main study informed consent to undergo screening for leukapheresis within 42 days prior to the day of the scheduled leukapheresis procedure. Patient must be deemed eligible based on inclusion / exclusion criteria for leukapheresis eligibility screening listed in Section 5.

4.1.1.1. Screening under other GSK studies

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

Where a participant was previously tested for HLA and/or NYESO-1 expression under a different GSK-sponsored protocol, testing of HLA and/or NY-ESO-1 for 208471 may not be required dependent on the test platform(s) used and whether they meet the 208471 protocol requirements. If the 208471 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 acceptable, in consultation with the Sponsor. Additionally, if lete-cel is already manufactured for these participants, leukapheresis and/or re-manufacture process may not be necessary, in consultation with the Sponsor.

4.1.2. Part 2: Leukapheresis/Manufacture

Participants who fulfill the leukapheresis eligibility criteria (Section 5) can undergo leukapheresis. The initiation of leukapheresis procedure constitutes enrollment in the study.

Disease progression may be present but is not mandatory for leukapheresis. In addition, leukapheresis may occur before, during or upon completion of a prior line of therapy, if appropriate washout periods are followed (See Table 12).

Upon development of progressive disease in metastatic cancer patients, the disease may have a rapid course, and any treatment delay can limit the treatment effect.

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

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

Consult with Sponsor for current shelf-life specifications of the cryopreserved T-cell product from leukapheresis and the cryopreserved drug product, lete-cel.

Following leukapheresis, lete-cel manufacture can be undertaken by the Sponsor as production slots become available. Additional details are provided in the Apheresis Manual.

Supportive local therapy (e.g., radiotherapy, cryotherapy), chemotherapy, or other systemic treatments such as, but not limited to, PD-1/PD-L1 checkpoint blockers may be administered between leukapheresis and treatment if a participant has progressive disease and cannot be treatment-free. In this case, mandatory wash-out periods (Table 12) must be respected.

An intermediate SoC line of therapy between leukapheresis (Part 2) and treatment (Part 3) at the time of disease progression is allowed if all of the conditions in Section 6.2 are met.

4.1.3. Part 3: Lymphodepletion/Treatment (Interventional Phase)

In Arms A and B, lete-cel will be infused after having failed at least one line of PD-1/PD-L1 checkpoint blockade therapy.

For participants in Arm C, lete-cel will be infused after having failed SoC targeted therapies (per NCCN or equivalent country guidelines [e.g., ESMO, NICE, etc.], as applicable).

Following clinical and/or radiographic evidence of disease progression, participant's fitness for lymphodepletion will be assessed, lymphodepletion eligibility criteria will be confirmed, and baseline tumor assessments (scan and biopsy) obtained prior to initiating the lymphodepleting chemotherapy. A baseline scan demonstrating measurable disease is required prior to lymphodepletion and before the participant will receive lete-cel; thereafter, the tumor will be followed as per RECIST v1.1, starting at Week 7 per protocol.

Once the manufactured lete-cel product has been received and the integrity of the bag(s) has/have been verified by the site, each participant will undergo lymphodepletion with cyclophosphamide and fludarabine (Section 6.3) in preparation for infusion of lete-cel on Day 1 (Section 6.4). Participants should receive Granulocyte-Colony Stimulating Factor (G-CSF) support and Mesna (Refer to Table 14 and Appendix 9).

On the day of lete-cel infusion, participants will be premedicated against potential infusion reactions with antihistamines and acetaminophen (paracetamol). Follow institutional guidance for dosage and specific medications (see Section 6.4.1 for details).

In Arms B and C, the first pembrolizumab administration is on Day 22 (Week 4 Day 1), then Q3W up to 35 cycles or disease progression, as described in Section 6.5. If pembrolizumab cannot be started at Week 4 due to an AE, participants assigned to Arm B or Arm C may receive their first dose of pembrolizumab on Week 7 Day 1, as long as permitted per Table 15.

The second dose of pembrolizumab will be administered 3 weeks later if the participant is not experiencing AEs as described in Section 6.5.

Participants will be frequently monitored for any unexpected ≥ Grade 3 AE / SAE; participants treated in Arms B and C will also be monitored for pembrolizumab treatment limiting toxicities (TLTs) as outlined in Section 8.3.2.

Participants in Arm A who have PD following treatment with lete-cel at or before the scheduled Week 25 scan may be offered pembrolizumab therapy (Part 4) following assessment of eligibility for pembrolizumab treatment, benefit-risk evaluation, and approval by the Sponsor's Medical Monitor (or designee).

Participants who are not eligible for study treatment by the time NY-ESO-1 specific (c259) T cells expire, will be withdrawn from the study and will not undergo lymphodepletion within this study.

For participants who withdraw from the study or die prior to receiving GSK3377794, any remaining apheresis or drug product from the participant will be stored by the Sponsor for up to 15 years (or according to local regulations) following the participant's withdrawal from the study or death. During this time, these materials may be used for scientific research at the Sponsor's discretion. After 15 years of storage, any materials which have not been used may be destroyed.

4.1.4. Part 4: Pembrolizumab Therapy Following Disease Progression after Lete-cel Infusion (for Arm A ONLY)

Participants in Arm A who have PD following treatment with lete-cel at or before the scheduled Week 25 scan, may be offered pembrolizumab therapy (Part 4) following assessment of eligibility for pembrolizumab treatment, benefit-risk evaluation, and approval by the Sponsor's Medical Monitor (or designee).

4.1.5. Part 5: Long-Term Follow-Up (LTFU)

Upon completing the interventional phase of the study (Part 3 or 4) but no sooner than 90 days post T-cell infusion (in order to capture enough safety information) or upon early withdrawal from the interventional phase, participants will be entered into a separate long-term follow-up (LTFU) protocol (GSK study 208750) and will be monitored for the observation of delayed AEs and survival during the 15 years post-infusion, in accordance with FDA regulations [FDA, 2020b] (Section 8.1.2). If not yet enrolled in Study 208750, there is a short-term provision (≤6 months) to follow participants according to the LTFU schedule under this protocol (reproduced on Table 8) until enrolled in the 208750 study. Participants who fail to consent to the 208750 study within this period will be withdrawn from Study 208471.

4.2. Scientific Rationale for Study Design

The study will employ an adaptive design to compare experimental therapy alone, or in combination with pembrolizumab, using Bayesian methods to provide probability of success estimates. The design provides efficiencies in the evaluation of experimental therapy by discontinuing arms that meet pre-defined futility thresholds at interim time-points while continuing enrollment to arms that may be more efficacious and subsequently graduate to Phase 3 confirmatory studies.

4.3. Justification of Dose

4.3.1. Justification of Lymphodepleting Regimen

The planned lymphodepleting regimen is fludarabine, 30 mg/m^2/day x 4 days and cyclophosphamide, 900 mg/m^2/day x 3 days, with lete-cel infusion on Day 1. This regimen is based on prior experience with lete-cel in participants with synovial sarcoma and melanoma, where fludarabine-containing regimens were associated with optimal responses [Mackall, 2016; Robbins, 2015]. For participants ≥60 years old, the lymphodepleting regimen should be adjusted as described in Section 6.3. For subjects with a prior history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia) or other risk factors, the investigator should discuss with the sponsor's

medical monitor or designee to determine the need for dose modification of the lymphodepletion regimen (see Section 6.3).

4.3.2. Justification of Lete-cel Dose

Lete-cel has achieved objective responses without significant toxicity, a dose range of 1 x 10^9 to 8 x10^9 total transduced T cells, in participants with metastatic synovial sarcoma, metastatic melanoma [Robbins, 2015] and multiple myeloma [Rapoport, 2015] whose tumors expressed the NY-ESO-1 or LAGE-1a antigens and who met the HLA inclusion criteria. This cell dose range was included in prior protocol amendments for Study 208471.

Optimization of the dose range:

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

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

Patients have previously been treated at this upper end of the revised dose range: in 2 older pilot studies (synovial sarcoma Study 208466 and multiple myeloma Study 209393), 3 patients received doses $>8 \times 10^9$ (up to 14.4×10^9) transduced T cells with no safety signals identified.

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

Since no dose-toxicity relationship has been established to date on 125 patients dosed with lete-cel (GlaxoSmithKline Document Number: RPS-CLIN-015027), it is anticipated that the safety profile in patients who receive doses up to the theoretical 15×10^9 transduced cells will remain comparable to the current safety profile.

- For participants treated as of protocol amendment 7, any released manufactured product counting between (1-15) $\times 10^9$ transduced cells will be shipped in its entirety for infusion as a single dose.

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

4.3.3. Justification of Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W, which is the current approved dose and schedule for pembrolizumab. Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is the appropriate dose of

pembrolizumab for adults across all indications and regardless of tumor type. This dose is justified by:

- clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.3.1. Justification for Administration of First Dose of Pembrolizumab on Day 22 Following Lete-cel Infusion

In Arms B and C, pembrolizumab administration starts on Day 22 (if deemed safe), and repeated Q3W for up to 35 cycles or disease progression (see Section 6.5). The rationale

for starting pembrolizumab administration on Day 22 is to minimize the risk of CRS and ensure adequate bone marrow recovery following lymphodepletion.

4.4. End of Study Definition

The completion of the interventional phase of the study is defined as the date when at least 70% of all participants who received lete-cel infusion (mITT) have progressed, died or have been lost to follow-up.

The study ends when all participants who received lete-cel infusion (mITT) have moved to the separate LTFU protocol, declined LTFU, have been lost to follow-up, withdrew early, or died.

4.4.1. End of Interventional Phase/Study for Individual Participants

End of interventional phase for individual participants

Participants who do not receive pembrolizumab will be considered to have completed the interventional phase of the study (Part 3 or 4) after being on study until Week 106 post lete-cel infusion (approximately 2 years), confirmed disease progression (as defined by CCI), or death (whichever occurs first) in order to allow for the primary analysis to occur. Participants who receive pembrolizumab in Arms B or C, or in Arm A following disease progression after lete-cel infusion (Part 4), will be considered on the interventional phase of the study until completion of 35 cycles of pembrolizumab, confirmed disease progression in Arms B and C (as defined by CCI), further confirmed disease progression in Arm A Part 4 (as defined by CCI), or death (whichever occurs first).If participant discontinues the interventional phase for reasons not listed above and does not withdraw from the study, they will be considered as having withdrawn from the interventional portion of the study.

Participants will complete an End of Treatment visit, as detailed in Table 7, unless withdrawn from the study.

Upon completing the interventional phase of the study (Part 3 or 4) but no sooner than 90 days post T-cell infusion (in order to capture enough safety information) or upon early withdrawal from the interventional phase, participants will be entered into a separate long-term follow-up (LTFU) protocol (GSK Study 208750) and will be monitored for the observation of delayed AEs and survival during the 15 years post-infusion, in accordance with FDA regulations [FDA, 2020b] (Section 8.1.2). If not yet enrolled in the LTFU protocol, participants who have not withdrawn from this study will be followed per LTFU schedule under this protocol (Part 5) until enrolled in LTFU protocol (see Table 8).

End of study for individual participants

The study 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, withdrawn from the study, or died.

Discontinuation of pembrolizumab does not represent withdrawal from the interventional phase or withdrawal from the study. Refer to Section 7.1 for more information.

5. STUDY POPULATION

This Phase 1b/2a study aims to evaluate safety and clinical activity of lete-cel, alone (Arm A) or in combination with pembrolizumab (Arms B and C) in participants with cytologically or histologically confirmed advanced Stage IIIb or IV or recurrent NSCLC.

Prospective approval of protocol deviations from recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Inclusion/Exclusion criteria are grouped into 4 parts and eligibility screening will take place in the following 4 steps:

- **Target expression screening:** A set of criteria permitting participants' blood to be screened for HLA-type and tumor sample to be screened for the expression of NY-ESO-1/LAGE-1A.
- **Leukapheresis eligibility screening:** To be fulfilled prior to performing leukapheresis procedure.
- **Lymphodepletion eligibility screening:** To be fulfilled prior to performing lymphodepletion procedure.
    - **Treatment fitness:** To be evaluated prior to commencing lymphodepleting chemotherapy and administration of lete-cel.
- **Pembrolizumab treatment screening** (Arm A ONLY, Part 4): To be fulfilled prior to commencing pembrolizumab treatment among patients in Arm A who progress following administration of lete-cel.

5.1.1. Target Expression Screening

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

1. The participant (or legally acceptable representative if applicable) provides written informed consent for the screening process described as "Target Expression Screening" in the SoA (Section 1.3).
2. Age ≥18 years on the day of signing informed consent.
3. Medical Monitor (or designee) approval has been obtained if participants are enrolled or to be enrolled in other experimental interventional clinical studies during the screening and leukapheresis stages of this study (GSK208471).
4. Histologically or cytologically diagnosed unresectable Stage IIIb or Stage IV NSCLC.
    a. Arms A and B: Participants with NSCLC lacking actionable genetic aberrations (i.e., wild type) per NCCN guidelines, based on SoC diagnostic test.

b. Arm C: Participants with NSCLC with actionable genetic aberrations (e.g., sensitizing EGFR mutation ALK translocation, etc.) per NCCN guidelines, based on SoC diagnostic test.

5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
6. Tumor tissue sample with associated pathology report is available to perform tumor antigen expression analysis (NY-ESO-1 or, if tested, LAGE-1a), in alignment with Section 8.9.2.

   Note: Participants may not need to repeat certain screening/baseline assessments or procedures if performed as part of other GSK studies (see Section 4.1.1.1).

5.1.2. Leukapheresis Eligibility Screening

All screening criteria described in Section 5.1.1 must be reviewed and fulfilled along with all the following criteria prior to leukapheresis. Leukapheresis process may not be necessary for participants for which lete-cel cell product is already manufactured. Additionally, participants may not need to repeat certain screening/baseline assessments or procedures if performed as part of other GSK studies (see Section 4.1.1.1).

7. The participant has successfully completed the HLA and target expression evaluations.
   a. Participant is positive for any of the following alleles: HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 by a validated test.
   b. Participant's tumor has been reviewed by the GSK-designated laboratory and confirmed as meeting the pre-defined threshold for expression of NY-ESO-1 and/or, if tested, LAGE-1a.

After HLA allele genotyping and tumor antigen expression have been found positive, an eligible participant must fulfill all the following inclusion criteria:

8. Participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
9. Participant must have adequate organ function and blood cell counts as indicated by the laboratory values in Table 11 and within the appropriate time windows per Schedule of Activities Table 2 (and per Table 3 for Treatment fitness assessment).

Table 11 Adequate Organ Function

System	Laboratory Values
Hematologic[a,b,c]	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L (without granulocyte colony-stimulating factor)
Absolute lymphocyte count (ALC)	≥0.5 x 10^9/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (not achieved by transfusion)
Platelets	≥100 x 10^9/L (not achieved by transfusion)
Hepatic	
Albumin	≥3.5 g/dL
Total bilirubin Participants with Gilbert's Syndrome (only if direct bilirubin ≤35%)	≤1.5 x upper limit of normal (ULN) (isolated bilirubin ≥1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
Alanine aminotransferase (ALT)	≤2.5 x ULN (or ≤5 x ULN if documented history of liver metastases)
Renal	
Calculated creatinine clearance (CrCl)	≥50 mL/min

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

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

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

    $$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [if\ female] \times 1.159\ [if\ black]$$

    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 may be required for cyclophosphamide, see Section 6.3 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.

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 platelet transfusions within 14 days.
b. No red blood cell transfusions to meet minimum hematologic values for eligibility.
c. Organ function will be reassessed prior to **lymphodepletion**: if, upon consultation with the Medical Monitor, there is evidence from laboratory values that recovery from last anti-cancer treatment is underway, hematology labs may be considered acceptable and requirements waved to proceed with lymphodepletion.
d. Prior to **lymphodepletion**, please refer to Section 6.9.2 for guideline on use of anticoagulant medications.

10. Predicted life expectancy that is ≥24 weeks from leukapheresis.
11. Participant has left ventricular ejection fraction ≥45%.
12. Participant is fit for leukapheresis and has adequate venous access for leukapheresis.
13. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    a. **Male Participants:**
    Male participants are eligible to participate if they agree to the following during the intervention period starting at the first dose of chemotherapy (lymphodepletion regimen) for at least 12 months after receiving the T-cell (lete-cel) 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:

    - If receiving pembrolizumab, must use effective contraception for at least 4 months after the last dose of pembrolizumab if this time frame is longer than the duration of contraception required in the context of chemotherapy (lymphodepletion regimen) and gene modified cells.
    - Refrain from donating sperm, PLUS, EITHER:
        - Abstain from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

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

    b. **Female Participants:**
    Female participants are eligible to participate if they are not pregnant or breastfeeding, and, at least 1 of the following conditions applies:

    - Is not a woman of childbearing potential (WOCBP) as defined in Section 5.3.3,
      OR
    - Is a WOCBP (as defined in Section 5.3.3) who will agree to use a barrier method (male condom) and use a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Section 5.3.3, during the intervention period and for at least 12 months after receiving the T-cell (lete-cel) 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. If the participant is planned to receive pembrolizumab, she must

use a barrier method (male condom) and a highly effective contraception (with a failure rate of <1% per year) for at least 4 months after the last dose of pembrolizumab if this time frame is longer than the duration of contraception required in the context of chemotherapy (lymphodepletion regimen) and gene modified cells. 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. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

5.1.3. Lymphodepletion Eligibility Screening

The following criteria must be confirmed within protocol pre-specified timelines (see Table 3).

14. Prior therapies

    a. All participants with NSCLC lacking actionable genetic aberrations (i.e., wild type), per NCCN guidelines (Arms A and B), need to have received at least one line of PD-1/PD-L1 checkpoint blockade therapy. For participants in the metastatic setting, PD-1/PD-L1 checkpoint blockade therapy must have been received either alone, in combination or sequentially with platinum-containing chemotherapy (adjuvant therapy will count as a regimen if completed within 6 months before the relapse).

    OR

    b. All participants with NSCLC with actionable genetic aberrations (e.g., sensitizing EGFR mutation ALK translocation, etc.), per NCCN guidelines (Arm C only), should have received appropriate targeted therapy following NCCN or equivalent country-level guidelines (e.g., ESMO, NICE, etc.). These participants could have received and failed PD-1/PD-L1 checkpoint blockade therapy.

    OR

    c. Medical Monitor (or designee) approval has been obtained if prior SoC therapy is refused by the participant (following discussion between participant and Investigator about benefits and risks)

    OR

    d. Participants not eligible for SoC anti-cancer therapy OR have terminated prior treatment due to intolerable side effects. Participants "intolerant" to an anti-cancer therapy are those who are either ineligible to receive anti-cancer therapy

OR have developed Grade ≥3 toxicity necessitating discontinuation of therapy, or dose modification, and/or Grade ≥3 unplanned hospitalization to alleviate effects of toxicity.

e. Experimental systemic regimens are allowed.

15. Disease progression:
    a. Lymphodepleting regimen may start after clinical AND/OR radiographic disease progression without second confirmatory imaging, based upon benefit-risk evaluation in agreement with the Medical Monitor (or designee).
    b. Following treatment with a PD-1/PD-L1 checkpoint blockade therapy administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies, progression is defined by meeting all of the following criteria:
        - Received at least 2 doses of an approved PD-1/PD-L1 checkpoint blockade therapy
        - Demonstrated progression after PD-1/PD-L1 therapy as defined by RECIST v1.1. In cases where pseudoprogression is suspected, the initial evidence of disease progression should be confirmed by a second assessment no less than 4 weeks and no more than 8 weeks after the date of the first documented progression, in the absence of rapid clinical progression [Seymour, 2017]. Confirmatory imaging may not be required based upon a benefit-risk evaluation in agreement with the Medical Monitor (or designee).
    c. An intermediate SoC line of therapy between leukapheresis (Part 2) and treatment (Part 3) at the time of disease progression is allowed if all of the conditions in Section 6.2 are met.
16. Measurable disease per RECIST v1.1 as assessed by local site investigator/radiology.

    Measurable disease, i.e., presenting with at least one measurable lesion per RECIST v1.1. See Section 10.10.1 for definition of a measurable lesion.

    Note: Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
17. Participant has undergone mandatory washout periods (Table 12) if receiving supportive therapy (e.g., radiotherapy, cryotherapy, chemotherapy, or other systemic treatments).
18. A hematologist has been consulted prior to lymphodepletion in participants who have had a serious/significant bleeding/thrombosis history.

5.1.3.1. Treatment Fitness

Given potential changes in clinical status between screening/enrollment and the start of conditioning chemotherapy, safety assessments from Section 5.1.1 and Section 5.1.2 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.

5.1.4. Pembrolizumab Therapy Following Disease Progression after Lete-cel Infusion (Arm A ONLY, Part 4)

Participants who have received lete-cel in Arm A are eligible for therapy with pembrolizumab 200 mg flat dose Q3W if they fulfill all the following criteria:

19. Radiographically confirmed progressive disease following treatment with lete-cel at or before the scheduled Week 25 scan.
20. Any toxicity must be ≤ Grade 1 CTCAE (v4.03) at the time of first/dose (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Participants with Grade 2 toxicities that are deemed stable or irreversible (e.g., non-demyelinating peripheral neuropathy) can be enrolled on a case-by-case basis with prior consultation and agreement with the Sponsor's Medical Monitor (or designee).
21. Pembrolizumab treatment is permitted, following benefit-risk evaluation between the Investigator and Sponsor's Medical Monitor (or designee).

5.2. Exclusion Criteria

5.2.1. Target Expression Screening

Participants are not eligible to be screened for target expression if any of the following criteria apply:

1. Prior treatment:
    a. Previous treatment with genetically engineered NY-ESO-1-specific T-cells.
    b. Previous NY-ESO-1 vaccine or NY-ESO-1 targeting antibody.
    c. Prior gene therapy using an integrating vector.
    d. Previous allogeneic hematopoietic stem cell transplant.
2. Prior malignancy other than NSCLC, with the following exceptions:
    a. Participants with a history of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.
3. Participant has undergone prior allogeneic/autologous bone marrow or solid organ transplantation.

5.2.2. Leukapheresis Eligibility Screening

Participants are not eligible for leukapharesis if any of the Exclusion criteria in Section 5.2.1 apply. Please note that mandatory washout period restrictions must be respected (Table 12) before starting leukapheresis. In addition, participants are not eligible for leukapheresis if any of the following criteria apply:

4. Participant has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to cyclophosphamide, fludarabine, dimethylsulfoxide (DMSO) or other agents used in the study (participants with vitiligo or resolved childhood asthma/atopy are an exception to this rule).
5. Participant has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
6. Participant has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
7. Participant has a history of chronic or recurrent (within the last year prior to enrollment) severe autoimmune or active immune-mediated disease requiring steroids or other immunosuppressive treatments.
8. Uncontrolled intercurrent illness including, but not limited to:
    a. Ongoing or active infection (including but not limited to systemic fungal infections)
    b. Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class >1
    c. Uncontrolled clinically significant arrhythmia in last 6 months
    d. Acute coronary syndrome (angina or myocardial infarction) in last 6 months
    e. Severe aortic stenosis, symptomatic mitral stenosis
    f. Inadequate 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])
    g. Interstitial lung disease (participants with existing pneumonitis as a result of radiation are not excluded; however, participants cannot be oxygen dependent) **Note**: Post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed upon by the Investigator and Sponsor's Medical Monitor (or designee).
    h. Prior or active demyelinating disease
    i. Current unstable liver or biliary disease per Investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.
9. Participant has active infection with HIV, HBV, HCV, EBV, CMV, syphilis, or HTLV as defined below:
    a. Positive serology for human immunodeficiency virus (HIV).
    b. 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.

c. 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.

d. Positive serology for human T lymphotropic virus 1 or 2 (HTLV-1 or -2).

e. Positive serology for Epstein-Barr virus (EBV). Participants with positive EBV serology will undergo additional tests/assessments in order to rule out active infection.

f. Active CMV infection. Participants with positive CMV serology need to undergo additional tests/assessments in order to rule out active infection.

g. Positive test for syphilis (spirochete bacterium).

10. Participant is pregnant or breastfeeding.
11. Participant has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating Investigator and in agreement with the Sponsor's Medical Monitor (or designee).
12. Participant has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study
13. QTc >480 msec.

    Notes:

    a. Collect a single ECG. If QTc is >480 msec, collect 2 more ECGs 5 minutes apart and use the average of those QTc values to determine eligibility. If the average QTc is >480msec get a manual overread of the triplicate.

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

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

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

14. Prior/Concomitant Therapy:

    a. Toxicity from previous anti-cancer therapy that has not recovered to CTCAE v4.03 Grade ≤1 prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Participants with existing pneumonitis

because of radiation are not excluded; however, participants cannot be oxygen-dependent. Participants with Grade 2 toxicities that are deemed stable or irreversible (e.g., peripheral neuropathy) can be enrolled on a case-by-case basis with prior consultation and agreement with the Sponsor Medical Monitor (or designee).

b. Other standard of care lines of therapy are allowed only if guidelines and washout periods are followed as described in Table 12.

15. Investigational treatment within 4 weeks or 5 half-lives (whichever is shorter) prior to leukapheresis (or lymphodepletion). Investigational vaccines (other than NY-ESO-1 vaccines that are not allowed) must follow the washout period specified in Table 12 Exceptions to this rule must be evaluated by the Investigator in agreement with the Sponsor's Medical Monitor (or designee).
16. Symptomatic or untreated central nervous system (CNS) metastases.

    Participants with treated asymptomatic CNS metastases (supratentorial or cerebellar) may be eligible after discussion and agreement with the Sponsor Medical Monitor (or designee), and if they meet all 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 if any radiotherapy was administered after the screening MRI

    Participants who develop oligometastatic CNS metastasis (supratentorial or cerebellar) after leukapheresis and prior to the 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 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

5.2.3. Lymphodepletion Eligibility Screening

Please note that mandatory washout period restrictions must be respected (see Table 12) before starting lymphodepletion. In addition, participants meeting any of the following exclusion criteria cannot proceed with lymphodepleting chemotherapy and subsequent lete-cel treatment:

17. Manufactured T cells have expired their shelf life (consult with Sponsor for current shelf life specifications).
18. Participant has received treatment/therapy within the required washout periods listed in Table 12.
    a. Participants must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 non-demyelinating neuropathy are eligible.

    Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
19. 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: Electron beam radiotherapy to superficial structures in the chest is permitted. There is no wash-out period for palliative radiation to non-target lesions other than the lung and mediastinum.
20. Participant has received ≥50 Gy radiotherapy to a significant volume of the pelvis, long bones or spine, or a cumulative dose of radiation that, in the investigator's opinion would predispose patients to prolonged cytopenia after lymphodepletion.
21. All of the participant's measurable lesions have been irradiated within 3 months before lymphodepletion.
    Note: An irradiated measurable lesion with unequivocal progression following irradiation may be considered a target lesion regardless of time from last radiotherapy dose.
22. Participant has undergone major surgery ≤28 days before the first dose of study treatment.
23. Active infection requiring intravenous systemic therapy.

Table 12 Concomitant Treatments and Washout Periods

Treatment/Therapy[1]	Required Washout prior to leukapheresis and lymphodepletion
Cytotoxic chemotherapy	2 weeks
Immune therapy (including monoclonal antibody therapy)	No wash-out for PD-1/PD-L1 checkpoint blockade agents. For all others, case by case evaluation between Investigator and Sponsor's Medical Monitor (or designee).
Anticancer Vaccine	2 months The participant should be excluded if the Investigator considers the participant's disease to be responding to an experimental vaccine given within 6 months.
Live-virus vaccination (seasonal flu vaccines that do not contain live virus are acceptable).	4 weeks
Systemic corticosteroids or any other immunosuppressive therapy NOTE: Use of inhaled or topical steroids or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency is acceptable.	2 weeks
Investigational treatment	4 weeks or 5 half-lives[2]
Tyrosine kinase inhibitors	1 week[3]
Radiotherapy	See exclusion criteria #19, #20 and #21, prior to lymphodepletion[4]
Herbal medications and other dietary supplements	2 weeks (see Section 6.9 for details)

Abbreviation: PD-1/PD-L1 = programmed death protein 1/PD-1 ligand.

1. Permission and washout for any other anticancer therapies must be discussed with the Sponsor's Medical Monitor (or designee).
2. Washout period of 4 weeks or 5 half-lives, whichever is shorter.
3. One-week washout period for tyrosine kinase inhibitors prior to lymphodepletion. No required washout period prior to leukapheresis.
4. No required washout period prior to leukapheresis.

5.2.3.1. Treatment Fitness

Given potential changes in clinical status between screening/enrollment and the start of conditioning chemotherapy, safety assessments from Section 5.2.1 and Section 5.2.2 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.

5.2.4. Pembrolizumab Therapy Following Disease Progression after Lete-cel Infusion (Arm A ONLY, Part 4)

24. Persistence of toxicities such as CRS ≥ Grade 2 that preclude treatment with pembrolizumab.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2. Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading, walking slowly, sitting at a computer, making the bed, eating, preparing food, and washing dishes).

5.3.3. Contraception

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

5.3.3.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

I. Premenarchal female

II. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

III. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range (as per laboratory parameters for postmenopausal range) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT) when postmenopausal status is in doubt. However, in

the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

5.3.3.2. Contraception

Male Participants

Male participants must agree to the following during the intervention period starting at the first dose of chemotherapy (lymphodepletion regimen) 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. If assigned to Arm B or Arm C or participating in Part 4 Arm A, participants must use effective contraception for at least 4 months after the last dose of pembrolizumab if this time frame is longer than the duration of contraception required in the context of chemotherapy (lymphodepletion regimen) and gene modified cells.

- Refrain from donating sperm

Plus either:

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

OR

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

Female Participants

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

Table 13 Contraceptives Allowed During the Study

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User-Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Highly Effective Methods[b] That Are User-Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o Oral o Intravaginal o Transdermal o Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o Oral o Injectable
• Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

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

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 12 months after receiving 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. Participants assigned to Arm B or Arm C or participating in Part 4 Arm A must also use effective contraception for at least 4 months after the last dose of pembrolizumab if this time frame is longer than the duration of contraception required in the context of chemotherapy (lymphodepletion regimen) and gene modified cells. If there is any question that a participant of childbearing potential

will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.4. Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with lete-cel or pembrolizumab, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

5.3.5. Use in Nursing Women

It is unknown whether lete-cel or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.4. 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 SAEs.

Individuals who do not meet the criteria for participation in this study (any screen failure except for HLA) may be rescreened 1 additional time. Rescreened participants should be assigned a new participant number.

6. STUDY INTERVENTION

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

6.1. Leukapheresis

Participants who complete screening procedures and meet all eligibility criteria will be eligible to undergo leukapheresis to obtain the starting material for the manufacture of autologous lete-cel.

For collection of the starting material, a large-volume non-mobilized peripheral blood mononuclear cell (PBMC) collection should be performed according to institutional standard procedures and as detailed in the Apheresis Manual. In cases where the minimum number of PBMCs is not collected or the manufactured lete-cel product cannot be infused back to the participant, a second leukapheresis may be performed. The collected leukapheresis product will then be transported for manufacture as detailed in the Apheresis Manual.

6.2. Supportive Therapy and/or SoC Therapy Before Lymphodepletion

Supportive local therapy (e.g., radiotherapy, cryotherapy, etc.), chemotherapy, or other systemic treatments may be administered between Screening and leukapheresis, and between leukapheresis and the start of lymphodepletion (bridging therapy) if a participant has progressive disease and cannot be treatment-free, but mandatory washout periods (Table 12, Section 5.1 and Section 5.2) must be respected. For therapies not described in this protocol, wash-out periods should be around 4 weeks or 5 half-lives (whichever is shorter), in consultation with Medical Monitor for the study.

A SoC line of therapy may be administered to participants before lymphodepletion based on the Investigator's evaluation of benefits and risks, in accordance with local regulatory requirements and standards, and in agreement with the Sponsor's Medical Monitor (or designee).

An intermediate SoC line of therapy between leukapheresis (Part 2) and treatment (Part 3) at the time of disease progression is allowed if it is based on benefit-risk assessment and/or local regulatory requirements and following agreement with Sponsor's Medical Monitor (or designee).

> Note: SAEs related to study participation and other clinical observations affecting treatment eligibility need to be reported in this study database.
>
> Note: Participants receiving a line of systemic SoC treatment can start lymphodepletion after disease progression.

6.3. Lymphodepleting Chemotherapy

Once lete-cel has been manufactured and received at the site, eligible participants will proceed to have lymphodepleting chemotherapy and infusion of lete-cel as detailed in this section.

Prior to the administration of lymphodepleting chemotherapy, participant's fitness for lymphodepletion will be assessed together with the Medical Monitor and baseline tumor assessments (scan and biopsy) obtained (See Section 1.3 for Schedule of Activities).

When the lete-cel cells have been manufactured, have fulfilled release criteria, and are available for infusion at the site, lymphodepleting fludarabine and cyclophosphamide can be administered as described in Table 14. Cyclophosphamide and fludarabine will be supplied by the pharmacy of the participating institution.

Table 14 Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy					**Recommended prophylaxis and supportive medication**
Day	**Drug**	**Dose,[b] mg/m²**	**Route**	**Administration[d]**	**Infection**: On admission for lymphodepleting chemotherapy, commence anti-microbial and anti-fungal prophylaxis as recommended in Section 10.9.2 or in line with institutional standard practice. **Hydration**: Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions. **Mesna**: Should be given to prevent urotoxicity per institutional guidelines or as recommended in Section 6.3.4. **G-CSF**: Must start ~24 hours after the last cyclophosphamide infusion (i.e. on Day -4) until resolution of neutropenia in accordance with ASCO guidelines (Smith, 2015) or in line with institutional practice.
-8	Fludarabine[a]	30	IV	In 50 to 100 mL 0.9% NaCl over 30 mins[c]	
-7	Fludarabine[a]	30	IV	In 50 to 100 mL 0.9% NaCl over 30 mins[c]	
	Cyclophosphamide	900	IV	In 100 to 250 mL 0.9% NaCl over 1 hour	
-6	Fludarabine[a]	30	IV	In 50 to 100 mL 0.9% NaCl over 30 mins[c]	
	Cyclophosphamide	900	IV	In 100 to 250 mL 0.9% NaCl over 1 hour	
-5	Fludarabine[a]	30	IV	In 50 to 100 mL 0.9% NaCl over 30 mins[c]	
	Cyclophosphamide	900	IV	In 100 to 250 mL 0.9% NaCl over 1 hour	
-4	Start G-CSF[d]				
-3					
-2					
-1					
1	Lete-cel infusion[e]				

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

a. Fludarabine dose will be adjusted in renal impairment as described in Section 6.3.2. This adjustment needs to be applied to all doses, on top of the age-related modification. Fludarabine dose will not be adjusted by body weight per ASBMT guidelines that recommend dosing based upon body surface area (BSA) using total body weight [Bubalo, 2014], unless required otherwise by institutional guidelines.
b. Lymphodepleting regimen will be adjusted in participants ≥60 years old as described in Section 6.3.1.
c. Concentration ≤1 mg/mL.
d. Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF per institutional standard practice. If using pegylated G-CSF, give one dose ~24 hours after the last chemotherapy administered.
e. Administration of lete-cel is described in Section 6.4.

6.3.1. Lymphodepletion Dose Modification

Dose and regimen for lymphodepleting chemotherapy is adjusted for participants ≥60 years old, as follows:

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

Baseline assessments may be completed between Day -17 and Day -8 among participants who initiate the lymphodepleting regimen on Day -7.

The investigator must discuss with the sponsor's medical monitor or designee to determine the need for dose modification of the lymphodepletion regimen in situations such as but not limited to the following:

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

If during the course of lymphodepletion a participant experiences toxicity and is unable to complete the lymphodepletion regimen, participant may proceed with infusion in agreement with Medical Monitor.

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

Lymphodepletion dose calculation

For Investigators with patients approaching lymphodepletion, GSK requires that you review your Creatinine Clearance and Lymphodepletion 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 (CrCl, estimated or measured). Any significant discrepancy that would lead to a change in dose will be discussed with Investigator prior to commencing lymphodepletion.

Calculations methods are provided in Section 5.1.2 Table 11 Definitions of Adequate Organ Function, Renal for CKD-EPI and 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.

6.3.2. Fludarabine Dose Adjustment for Renal Impairment

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

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

Note: to estimate CrCl (in mL/min) please use Table 11 (Adequate Organ Function) for calculation steps before comparing to the thresholds given above.

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

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

6.3.3. Cyclophosphamide Dose Adjustment

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

6.3.4. Mesna

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

- 20% of cyclophosphamide dose (180 mg/m^2) x 4 doses at times 0 (start of cyclophosphamide infusion) and then 3 hours, 6 hours, and 9 hours after the start of each cyclophosphamide infusion.

6.4. T-cell (Lete-cel) Infusion

Lete-cel, autologous T-cells transduced with a self-inactivating lentiviral vector encoding an affinity enhanced TCR specific for NY-ESO-1/LAGE-1a, is one of the IPs in this study.

Participants will receive a single-dose of lete-cel five days after completing the lymphodepleting chemotherapy. This is considered Day 1 and all procedures and assessments to be performed are listed in the Schedule of Assessments (Section 1.3).

6.4.1. Premedication

Thirty (30) to 60 minutes prior to lete-cel infusion, participants will be premedicated against potential infusion reactions with antihistamines and acetaminophen (paracetamol). Follow institutional guidance for dosage and specific medications. **It is to be noted that steroids should not be administered as premedication for T-cell infusion because they are lymphotoxic and inhibitory to the T-cell product.**

6.4.2. Lete-cel Dose

A dose range of 1 x 10^9 to 15 x 10^9 total transduced cells will be administered by a single IV infusion on Day 1. If the transduced cell dose is less than the minimum dose of 1 x 10^9, manufacturing of additional transduced T-cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range.

In the event that no banked leukapheresis product is available, a second leukapheresis may be performed to achieve a dose in the target range. If after a second leukapheresis, manufacturing has still not produced at least the minimum target dose of 1 x 10^9 cells, and the patient still would like to be treated with their cells, the participant may be allowed to receive lete-cel following review and approval by the local IRB, regulatory agency, Investigator and Sponsor's Medical Monitor, if deemed clinically acceptable. In such cases however, it is expected that at least 5 x 10^8 cells would need to be available. These participants will be included in the safety population, but not in the Modified ITT (mITT) Population or All Evaluable Population (see Section 9.3).

6.4.3. Lete-cel Administration

Vital signs will be recorded prior to infusion (Table 3).

On Day 1, the participant will receive thawed lete-cel by IV infusion. Prior to infusion, two clinical personnel will independently verify and confirm in the presence of the

participant that the information on the infusion bag is correctly matched to the participant, as per the Sponsor's and clinical site's procedures.

A leukoreduction filter must not be used for the infusion of the T-cell product. The specific instructions for the preparation and administration of lete-cel are found in the Drug Product and Infusion Manual. Any deviations from the procedure detailed in the Drug Product and Infusion Manual should be recorded and reported accordingly.

In the event of an adverse reaction to cell infusion, the infusion rate should be reduced or stopped and the reaction managed according to institutional standard procedures (Section 10.9.1). 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 lete-cel infusion may be delayed in a participant with significant complications of 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 lete-cel infusion date. Cytopenias alone should not be a reason to delay lete-cel infusion unless complications are present.

Participants who have undergone leukapheresis but do not receive the lete-cel infusion will be replaced.

6.4.4. Pembrolizumab Therapy Following Disease Progression after Lete-cel Infusion (Part 4, Arm A Only)

Participants in Arm A who have PD following treatment with lete-cel at or before the scheduled Week 25 scan may be offered pembrolizumab therapy following assessment of eligibility for pembrolizumab treatment, benefit-risk evaluation, and approval by the Sponsor's Medical Monitor (or designee). Pembrolizumab treatment will be administered at 200 mg Q3W for up to 35 cycles or until subsequent disease progression. The first day of pembrolizumab administration will be considered Day 1 of the pembrolizumab therapy phase (Pembrolizumab Week 1 Day 1). General information regarding pembrolizumab infusion (Section 6.5) is also applicable to participants in Part 4 of Arm A.

The SoA for participants that receive pembrolizumab following disease progression after lete-cel infusion in Arm A is presented in Table 5.

CCI [redacted]

6.5. Pembrolizumab Infusion in Arms B and C and Part 4 Arm A

In Arms B and C, the first pembrolizumab administration is on Day 22 (Week 4 Day 1), and then it is administered Q3W for up to 35 cycles (up to Week 106) or until disease progression, whichever occurs first.

If toxicities are observed at Day 22 that preclude the administration of pembrolizumab treatment (such as CRS Grade ≥2 or GVHD), infusion of pembrolizumab will start on Week 7 Day 1 and continue Q3 weeks for up to 35 cycles (up to Week 109). If AEs do not resolve by Week 7 Day 1 (see Table 15 for details), pembrolizumab will not be administered and the participant will be evaluated until disease progression or EoT.

Participants who do not receive pembrolizumab by Week 7 must be discussed by the Investigator and the Sponsor's Medical Monitor (or designee) prior to initiating pembrolizumab at a later date; enrollment can continue until at least 15 participants are assigned in Arm B and have received pembrolizumab by Week 7 and at least 15 participants are assigned to Arm C and have received pembrolizumab by Week 7.

The following general information regarding pembrolizumab infusion is applicable to participants in Arms B and C and Part 4 of Arm A:

- Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.
- Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 [-5/+10] minutes).
- The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution.

6.5.1. Schedule Modification Guidelines for Pembrolizumab (Arms B and C and Part 4 of Arm A)

AEs (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Table 15 lists severe or life-threatening AEs and conditions that preclude the start of pembrolizumab treatment or require that pembrolizumab treatment be withheld for drug-related toxicities. If pembrolizumab cannot be started at Week 4 Day 1 due to an AE, participants assigned to Arm B or to Arm C may receive their first dose of pembrolizumab on Week 7 Day 1, as long as permitted per Table 15. When pembrolizumab is given after progressive disease in Arm A, the day of the first pembrolizumab dose is designated as Pembrolizumab Week 1 Day 1. See Appendix 9 for supportive care guidelines for management of pembrolizumab toxicities.

Dosing interruptions are permitted in cases of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays). Participants should be placed back on study therapy by the next scheduled infusion 3 weeks later, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6. Preparation/Handling/Storage/Accountability

It is the Investigator/institution's responsibility to establish a system for handling both IPs (lete-cel and pembrolizumab) to ensure that:

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 IP received and any discrepancies are reported and resolved before use of the IP.
3. The participant's T-cell product (lete-cel) received at the site from the manufacturer will be stored at ≤ -130°C until ordered by the Investigator (or designee) to be infused.
4. Only participants enrolled in the study may receive IP and only authorized site staff may supply or administer IP. All IP 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.
5. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of unused IP are provided in the SRM and/or Drug Product and Infusion Manual.
    - Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor, and/or GSK study contact.
    - A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions will either be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the IP.

6.7. Measures to Minimize Bias: Randomization and Blinding

This is an open-label (unblinded) study. This study does not include randomization. Upon completion of the required screening assessments, eligible participants will be registered into the Registration and Medication Ordering System (RAMOS), the GSK Interactive Response Technology (IRT), by the investigator or authorized site staff. RAMOS allows study sites to register and assign participants. Arm assignment will be done centrally using an assignment schedule generated by the GSK Clinical Statistics Department, which will assign all participants with NSCLC lacking actionable genetic aberrations into Arm A or Arm B and all participants with NSCLC with actionable genetic aberrations (per NCCN guidelines), to Arm C.

6.8. Study Intervention Compliance

Lete-cel and pembrolizumab will be intravenously administered to participants at investigational sites by trained personnel. Administration will be documented in source documents and reported in the electronic case report form (eCRF).

6.9. Concomitant Therapy

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, vitamins, probiotics, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- the reason for use
- dates of administration including start and end dates
- the dose and frequency

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

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme-inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Paracetamol / acetaminophen at doses of ≤2 grams/day is permitted for use any time during the study, unless prohibited by the Investigator.

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.

An intermediate SoC line of therapy between leukapheresis (Part 2) and treatment (Part 3) at the time of disease progression is allowed if all of the conditions in Section 6.2 are met.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor (or designee).

6.9.1. Prohibited Concomitant Medication and Treatment

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

Participants should also not undergo anti-cancer locoregional therapies, such as surgical resection or non-palliative radiation. In the case of participants with mixed responses (e.g. shrinking target lesions with new non-target lesion, mixed response, etc.), the use of

anti-cancer locoregional therapies should be discussed with the GSK medical monitor. If any non-protocol anti-cancer therapies are used before confirmation of disease progression, the participant will be considered as having met the primary endpoint for efficacy and will be rolled over to the LTFU study (GSK Study 208750) or to Part 5 of this study (if not yet enrolled in the LTFU study).

Supportive chemo- or local therapy (e.g., radiotherapy, cryotherapy, etc.) may be administered between leukapheresis and the start of lymphodepletion. In this case, mandatory wash-out periods (Table 12) must be respected.

An intermediate SoC line of therapy between leukapheresis (Part 2) and treatment (Part 3) at the time of disease progression is allowed if all of the conditions in Section 6.2 are met.

Systemic steroids may abrogate the effects of the T-cell therapy (lete-cel) and, therefore, are discouraged unless required to manage CRS (Section 10.9.5) or other significant immune-mediated AEs. According to local SoC or American Society of Clinical Oncology guidelines [Basch, 2011], steroids may be used as anti-emetics before cyclophosphamide but must be discontinued no later than 3 days prior to infusion of lete-cel. Topical steroids for cutaneous application, inhaled steroidal treatments, and physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency are permitted.

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

See Section 5.2 for wash-out and excluded treatments prior to leukapheresis or lymphodepleting chemotherapy.

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2) are not allowed during this trial. Administration of live vaccine during the period of infusion of fludarabine, cyclophosphamide or lete-cel, and for at least three months after last dose of any of these agents is prohibited. If there is a clinical indication for any medication specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this aspect 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 treatment requires the mutual agreement of the Investigator, the Sponsor, and the participant.

All concomitant medications received within 28 days prior to the first dose of pembrolizumab and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered beyond 30 days after the last dose of study treatment should be recorded if given as treatment for SAEs and AEs of special interest (AESIs) as defined in Section 8.4.4.

6.9.2. Permitted Concomitant Medication and Treatment

Lesion sites previously requiring radiotherapy should be recorded prior to lymphodepleting chemotherapy. Palliative radiation (e.g., for pain relief to non-measurable lesions, non-target lesions present at Baseline, etc.) is permitted during the study. However, lesion sites requiring radiotherapy after lete-cel infusion should be evaluated as to whether that indicates disease progression.

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 guidance such as the Centers for Disease Control and Prevention (CDC) Clinical Practice Guideline for Vaccination of the Immunocompromised Host. Before immunizing a participant against SAR-CoV-2 (COVID-19) it is requested that you contact the study Sponsor.

The following will be recorded on the appropriate eCRF pages:

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

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

Recommendations for participants on therapeutic anticoagulants:

• 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.

6.9.3. Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.10. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to study treatment.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.10. Dose Modification

6.10.1. Modification Guidelines for Lete-cel (All Treatment Arms)

Because lete-cel is administered as a single infusion in all treatment arms, dose modification is not applicable to lete-cel.

6.10.2. Guidelines for Pembrolizumab Withholding and Discontinuation

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours after completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 15.

AEs (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Table 15 lists severe or life-threatening AEs and conditions that preclude starting pembrolizumab treatment or require that pembrolizumab treatment be withheld for toxicities related to lete-cel or pembrolizumab. If pembrolizumab cannot be started at Week 4 Day 1 due to an AE, participants assigned to Arm B or to Arm C may receive their first dose of pembrolizumab on Week 7 Day 1, as long as permitted per Table 15. For participants in Part 4 of Arm A, the day of first pembrolizumab infusion is designated as Pembrolizumab Week 1 Day 1. See Appendix 9 for supportive care guidelines for management of pembrolizumab toxicities.

Pembrolizumab may be interrupted for situations other than treatment-related AEs. Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays). Participants should be placed back on study therapy by the next scheduled infusion 3 weeks later, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study

record. The treatment restart ICF will be signed only by participants who restart pembrolizumab after a temporary discontinuation.

Table 15 Dose Modification Guidelines and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Study Treatment

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less; the taper should take at least 4 weeks.
2. For situations in which pembrolizumab has been withheld, pembrolizumab can be resumed after the AE has been reduced to Grade 1 or 0 and the corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if the AE does not resolve within 12 weeks after the last dose or if corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and/or life-threatening immune-related AEs (irAEs), IV corticosteroid should be initiated and then followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity Grade or condition (CTCAE v4.03)	Action taken with regard to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participant for signs and symptoms of pneumonitis. Evaluate participant with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participant for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever). Monitor participant for signs and symptoms of bowel perforation (i.e., peritoneal signs and ileus). GI consultation and endoscopy to rule out colitis should be considered for participant with ≥ Grade 2 diarrhea if colitis is suspected. Participant with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be given via IV infusion.
	Grade 4, or recurrent Grade 3	Permanently discontinue		

Immune-related AEs	**Toxicity Grade or condition (CTCAE v4.03)**	**Action taken with regard to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitoring and follow-up**
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (weekly or more frequently until liver enzyme value returns to Baseline or is stable).
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	
Type 1 diabetes mellitus (T1DM) or hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participant with T1DM. Administer anti-hyperglycemic to participant with hyperglycemia.	Monitor participant for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor participant for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate.	Monitor participant for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per SoC.	Monitor participant for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor participant for changes in renal function.
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation of the participant to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold		

Immune-related AEs	Toxicity Grade or condition (CTCAE v4.03)	Action taken with regard to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 2, 3 or 4	Permanently discontinue	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation of the participant to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation of the participant to confirm etiology and/or exclude other causes.
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	Intolerable/persistent Grade 2	Withhold	Based on type and severity of AE, administer corticosteroids.	Ensure adequate evaluation of the participant to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include, but are not limited to, encephalitis and other clinically important iRAEs (eg. vasculitis and sclerosing cholangitis).		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
Cytokine release syndrome (CRS)	Grade 2 or 3	Withhold until Grade ≤1	See Table 24	See Table 24
	Grade 4	Permanently discontinue		
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Grade 1 persisting beyond 24 hrs or associated with concurrent Grade 2 CRS	Withhold until resolution	See Section 10.9.8	See Section 10.9.8
	Grade 3 or 4	Permanently discontinue		
Pancytopenia/aplastic anemia	See Section 10.9.7	See Section 10.9.7	See Section 10.9.7	See Section 10.9.7

Immune-related AEs	Toxicity Grade or condition (CTCAE v4.03)	Action taken with regard to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
Insertional oncogenesis	See Section 8.3.5	See Section 8.3.5	See Section 8.3.5	See Section 8.3.5
Replication competent lentivirus (RCL)	See Section 8.3.5	See Section 8.3.5	See Section 8.3.5	See Section 8.3.5
1. Withhold or permanently discontinue pembrolizumab at the discretion of the Investigator or treating physician. NOTE: When withholding of pembrolizumab is required because of Grade 3 or 4 immune-related endocrinopathy, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy (or metabolic control is achieved in the case of T1DM).				

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptoms; GI = gastrointestinal; ICANS=Immune Effector Cell-Associated Neurotoxicity Syndrome; irAE = immune-related AE; IV = intravenous; RCL = replication competent lentivirus; SJS=Stevens-Johnson Syndrome; SoC = standard of care; T1DM = type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis.

Table 16 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade (v4.03)	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion. Additional appropriate medical therapy may include, but are not limited to, the following: IV fluids; Antihistamines; NSAIDs; Acetaminophen; Narcotics. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hour to 50 mL/hour). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	At 1.5 hours (±30 minutes) prior to infusion of pembrolizumab, the participant may be premedicated with diphenhydramine 50 mg po (or equivalent dose of antihistamine). Also, acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic) may be given.
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	Stop Infusion. Additional appropriate medical therapy may include, but are not limited to, the following: Epinephrine**; IV fluids; Antihistamines; NSAIDs; Acetaminophen; Narcotics; Oxygen; Pressors, Corticosteroids. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. Participant is permanently discontinued from further study drug treatment. **In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside, and a physician must be readily available during pembrolizumab infusion. For further information, please refer to the CTCAE (v4.03) at http://ctep.cancer.gov.		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAID = non-steroidal anti-inflammatory drug.

In accordance with the FDA and European Medicines Agency (EMA) requirements for gene therapy clinical trials, all participants completing the Interventional Phase of the study will be rolled over to a LTFU protocol (GSK Study 208750) for observation of delayed AEs and survival for 15 years post lete-cel infusion. If not yet enrolled in the LTFU protocol, participants will be followed per LTFU schedule under this protocol (Part 5) until enrolled in LTFU protocol (see Table 8).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Lete-cel is administered as a single infusion and as such individual stopping rules apply only to those participants receiving pembrolizumab treatment.

Discontinuation of pembrolizumab does not represent withdrawal from the study.

Participants will receive pembrolizumab treatment as described in Section 6.4.4 and Section 6.5, unless one of the following events occurs: disease progression (as determined by RECIST v1.1), death, or unacceptable toxicity, including meeting stopping criteria for liver chemistry abnormalities defined in Section 7.1.1, and QTc prolongation defined in Section 7.1.2.

In addition, study treatment may be permanently discontinued for any of the following reasons:

a. Deviation(s) from the protocol
b. Withdrawal of consent by participant (or proxy)
c. Discretion of the Investigator
d. Participant is lost to follow-up
e. Closure or termination of the study
f. Intercurrent illness that prevents further administration of study treatment(s)
g. Recurrent Grade 2 pneumonitis
h. Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.

Treatment will be considered complete after 35 cycles (approximately 2 years) of pembrolizumab administration unless any of the above events occur.

Note: The number of treatments is calculated starting with the first dose of pembrolizumab.

The primary reason for permanent discontinuation of study treatment must be documented in the participant's medical records and eCRF. All participants who

discontinue study treatment will have safety assessments at the time of discontinuation, at the EoT visit (Table 7), and during additional follow-up in the LTFU protocol (GSK Study 208750) or Part 5 of this study (LTFU). See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention, and at the EoT visit.

Permanently discontinued participants will not remain in the study and will be rolled over into the LTFU protocol (GSK Study 208750) or Part 5 of this study (LTFU).

Group Pausing Criteria

Throughout the study, safety data will be reviewed on an ongoing basis by the internal SRT (Section 8.3.1).

All SAEs and ≥ Grade 3 AEs possibly associated with either lete-cel or pembrolizumab will be closely monitored. Additionally, periodic safety reviews will be undertaken by the Sponsor.

It is expected that AEs will occur frequently in this population due to the underlying disease and that these can be serious. The review of AEs, and any decision to prematurely stop participant enrollment, will be determined by the SRT and reviewed by the relevant IRB.

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

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

Premature study termination may occur if:

- The Investigator, Sponsor, Medical Monitor, SRT, or any independent review board or regulatory body decides for any reason that participant safety may be compromised by continuing the study.
- Premature study termination may occur if the Sponsor decides to discontinue the development of the intervention used in this study.

7.1.1. Liver Chemistry Monitoring Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and to evaluate liver event etiology. Liver stopping criteria for participants who have received pembrolizumab either as study treatment in Arms B or C

or as pembrolizumab therapy received after disease progression after lete-cel infusion in Arm A (Figure 1) are described in Table 15, Section 6.10.2.

Refer to Table 15 for stopping and monitoring details.

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

7.1.1.1. Liver Event Monitoring

Level 1 Monitoring

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

Table 17 Liver Chemistry Monitoring Criteria Level 1

Liver Chemistry Monitoring Criteria Level 1	
Criteria	**Actions**
ALT ≥3x ULN and ≥1.5x baseline value **but** ALT <5x ULN and <2x baseline value **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury, or hypersensitivity	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize, or return to within baseline. • If, during monitoring, ALT increases to ≥5xULN and ≥2x baseline value, or remains ≥3x ULN and ≥1.5x baseline value for ≥4 weeks, or if total bilirubin increases to ≥2xULN, refer to Level 2 monitoring guidance below. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GSK = GlaxoSmithKline (Sponsor); ULN = upper limit of normal.

Level 2 Monitoring

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

Table 18 Liver Chemistry Monitoring Criteria Level 2

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

Required Actions and Follow-Up Assessments

Actions	**Follow-Up Assessments**
• Report the event to GSK **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (pre-Gene Therapy) (see **MONITORING** below) **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow-up assessments within **24 hrs** • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline (pre-Gene Therapy) • A specialist or hepatology consultation is recommended **For all other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow-up assessments within **24 to 72 hrs** • Monitor participant at least weekly until liver chemistries resolve, stabilize or return to within baseline (pre-Gene Therapy)	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥2xULN • If possible, obtain peripheral blood to check for persistence of genetically modified cells • Obtain CBC with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, and other over the counter medications • Record alcohol use on the liver event alcohol intake eCRF **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRFs.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood cell (count); CPK = creatine phosphokinase; eCRF = electronic case report form; GSK = GlaxoSmithKline (Sponsor); HBsAg = hepatitis B surface antigen; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; RNA = ribonucleic acid; SAE = serious adverse event; ULN = upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for the subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

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

7.1.1.2. Study Intervention Restart or Rechallenge after Liver Stopping Criteria Are Met

If a participant meets liver chemistry stopping criteria, do not restart/rechallenge participant with study intervention unless:

GSK Medical Governance approval **is granted**

Ethics and/or IRB approval is obtained, if required, and

Separate consent for intervention restart/rechallenge is signed by the participant

Refer to Table 15 for details.

If GSK Medical Governance approval to restart/rechallenge participant with study treatment **is not granted**, then participant must permanently discontinue study treatment and roll over into the LTFU study (GSK Study 208750) or Part 5 of this study (LTFU) for additional follow-up assessments.

7.1.2. QTcF Stopping Criteria

The stopping and restarting criteria for QTcF abnormalities described in this section will be applicable only to participants who have received pembrolizumab either as study treatment (Arms B or C) or after disease progression after lete-cel infusion (Arm A; see Figure 1) because lete-cel is administered as a single dose.

In case of need to confirm QTcF prolongations, the QTcF should be based on the average of triplicate ECG readings obtained over a brief (e.g., 5 to 10 minutes) recording period.

If a participant meets the corrected QTcF interval duration criteria below, study treatment(s) will be discontinued:

- QTcF >530 msec (with or without underlying Bundle Branch Block),

OR,

- QTcF change from baseline of >60 msec

See the SoA (Section 1.3) for data to be collected at the time of intervention and discontinuation. After discontinuation from the study, the participant enters the LTFU protocol (GSK Study 208750) or Part 5 of this study (LTFU).

7.1.3. Temporary Discontinuation

Lete-cel is administered as a single dose via IV infusion. In the event of severe reactions potentially associated with liver toxicities during infusion, the infusion may be interrupted. Please refer to the current Drug Product and Infusion Manual for details of dose administration. Please refer to Section 8 for safety assessments and monitoring; Section 10.3 for reporting of adverse events; and Section 10.9 for supportive care guidance on T-cell infusion, CRS and other potential risks.

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

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

In participants with infusion-related reaction ≤ Grade 2, infusion may be restarted once resolved to < Grade 1, following instructions in the Drug Product and Infusion Manual.

Refer to 6.10.2 for information about pembrolizumab dosing interruptions.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the interventional portion of the study, if possible, an End of Treatment / Interventional Phase visit should be conducted, as shown in the SoA. See the SoA (Section 1.3) for data to be collected at the time of discontinuation from the interventional portion of the study and for any further evaluations that need to be completed at EoT. After discontinuation from the interventional portion of the study, the participant enters the LTFU study (GSK Study 208750) or, if not yet enrolled in 208750, Part 5 of this study (LTFU). See Section 4.1.5 for details.
- The participant will be permanently discontinued from the study once enrolled in the separate LTFU study (GSK Study 208750). Participants who fail to consent to the 208750 study within 6 months of completing the End of Treatment / Interventional Phase visit will be withdrawn from Study 208471.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before the withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator (or designee) must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as described in Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

All study assessments and their timings are summarized in Section 1.3:

Table 2: Screening

Table 3: Lymphodepletion and Treatment: Interventional Phase

CCI [redacted]

Table 5: Pembrolizumab Therapy Following Disease Progression after Lete-cel Infusion (Part 4 Arm A Only)

CCI [redacted]

Table 7: End of Treatment

Table 8: Long-Term Follow-Up

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

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

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

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

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

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

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

8.1.1. Tumor Response Assessments

Tumor assessments for response and progression will be evaluated according to RECIST v1.1 [Eisenhauer, 2009] and CCI [Seymour, 2017] (see Section 10.10.2). Diagnostic quality CT scan of chest/abdomen/pelvis with contrast is required as detailed in Section 1.3.

Imaging scans of the chest, abdomen, and pelvis should be performed at baseline (i.e., within 2 weeks before lymphodepletion) and all subsequent visits as indicated in SoA (Section 1.3). Brain imaging is required for all participants at baseline (within 4 weeks before lymphodepletion) and as clinically indicated thereafter (refer to Section 10.9.8). Acceptable imaging modalities for this study include:

- Diagnostic-quality CT scan with oral and/or IV iodinated contrast of the chest and abdomen/pelvis (CT is the preferred modality for tumor assessments)
- MRI of the abdomen/pelvis acquired before and after gadolinium contrast agent administration
- Non-contrast enhanced CT of chest/abdomen/pelvis if a participant is contraindicated for both CT and MRI contrast or if they have renal compromise
- Additional scans (CT/MRI) should be acquired for any other areas of suspected/known disease per site SoC, if clinically indicated
- Digital photographs of skin lesions including a ruler for estimating the size of the lesion

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

Investigators will assess tumor response according to CCI for clinical decision making (Appendix 10, Section 10.10.2) and for exploratory evaluations. Tumor measurements for each participant should be performed by the same Investigator or radiologist (to the extent that this is feasible).

To allow time for the immune response to become apparent and for potential transient inflammatory reaction of the disease to the treatment ('tumor flare'), response will not be assessed before 4 weeks post infusion of lete-cel unless there is unequivocal clinical evidence of deterioration. Responses should be confirmed by repeat imaging scan performed not earlier than 4 weeks and not later than the next scheduled imaging scan after the criteria for response was first met. Progression should be confirmed by repeat imaging scan performed not earlier than 4 weeks and not later than 8 weeks after the criteria for progression was first met. Determinations of disease progression will be based upon RECIST v1.1; however, for continuation of pembrolizumab participants will be followed by CCI.

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

A description of the adaptations and CCI process is provided in Appendix 10.

Digital copies of all (non-lossy compressed, preferably DICOM formatted) scans and photographs (with embedded rulers) must be maintained at the Investigative site as source documents. All scans (scheduled and unscheduled) are submitted electronically to the central imaging vendor for QC, storage, and potential analysis. The process for tumor imaging and transmission to the central imaging vendor are detailed in the Imaging Manual. Tumor imaging is strongly preferred to be acquired by IV/oral contrast enhanced CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the preferred modality for imaging the brain and spine. FDG PET/CT will be collected centrally if performed as part of the site's routine disease management, at Screening and whilst on study, but will not replace CT scans.

8.1.2. Long-Term Follow-up

All participants will be followed for survival and for 15 years after T-cell (lete-cel) infusion for observation of delayed AEs in accordance with FDA requirements for gene therapy clinical trials [FDA, 2020b; FDA, 2010]. Delayed AEs, will be collected in the Interventional Phase of the study until disease progression, as defined by CCI (see Section 10.10.2) and thereafter in the LTFU protocol (GSK Study 208750). If not yet enrolled in the LTFU protocol, participants will be provisionally followed per LTFU schedule under this protocol (Part 5) until enrolled in LTFU protocol (see Section 4.1.5 and Table 8).

Delayed AEs are defined as those events that fall into one or more of the 6 categories listed below and which occur either after disease progression or the last patient visit, whichever occurs first; and are considered related to GSK's gene modified cell therapy. Delayed AEs will be collected until 5 years have elapsed from last T-cell infusion, or until patient dies, withdraws consent or is deemed lost to follow-up. Delayed AEs will be recorded in the CRF if reported by the patient or investigator between years 6 – 15. Specifically, emergence of any of the following new clinical conditions reported or observed and the action taken will be reported to the Sponsor as a delayed AE:

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

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Neurological assessment for encephalopathy syndrome (ES) must be performed as described in the SoA (Section 1.3) and Section 10.9.8. Height (Screening only) and weight will also be measured and recorded.

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

8.2.2. Vital Signs

- Blood pressure, pulse measurements, respiratory rate, and body temperature should be assessed per institutional standards. These will be assessed as per the SoA (Section 1.3) and recorded in the eCRF. Methods per institutional standards should be consistent throughout the course of the study. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
- On lete-cel infusion day, pulse oximetry should be taken according to Table 3. On pembrolizumab infusion days, pulse oximetry should be taken pre- and post-infusion.

8.2.3. Cardiac Assessments

All cardiac assessments will be performed locally.

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

- An ECHO or MUGA scan will be performed at screening and baseline (Table 2 and Table 3) to determine eligibility. Additional scans will be performed only if clinically indicated. NOTE: the same method of cardiac evaluation must be used consistently for any follow-up scans.
- Serum troponin and NT-proBNP / BNP as markers for cardiac health will be assessed prior to initiation of lymphodepletion.

Reports of cardiac events in participants with cardiac or pericardial disease following treatment with lete-cel will continue to be monitored through normal proactive Pharmacovigilance.

The 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT,

and QTcF intervals. Refer to Section 7 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

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

- prior cardiac insult (ie, prior myocardial infarct and prior coronary revascularization)
- significant valvular disease
- low ejection fraction
- cardiomyopathy
- history of heart failure
- significant cardiac arrhythmias
- history of cardiac toxicity from prior therapies
- baseline tumor masses in close proximity to the cardiac muscle

must:

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

In these participants with clinically significant cardiovascular risk factors, all reports of cardiac events following T-cell infusion will be monitored through proactive pharmacovigilance to determine causality. Supportive treatment for these participants will be provided per standard clinical practice guidelines.

8.2.4. Pulmonary Assessments

Participants should be considered for pulmonary consultation prior to lymphodepletion, which may include pulmonary function tests.

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

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

and should include:

- Close monitoring of chest imaging, as clinically indicated
- Close monitoring of fluid balance

- Continuous cardiac telemetry monitoring.

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

8.2.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the Investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.

8.3. Safety Monitoring

Safety will be assessed in a continuous manner (See Appendix 9 for general considerations on supportive care).

The Sponsor will review the safety throughout the conduct of the study and share the data on a frequent basis with the Investigators (Investigator teleconference) and a Safety Review Team (SRT).

Safety data will be proactively reviewed for each participant and summarized by participant and in aggregate across participants by treatment arm. The toxicities observed will be reviewed in the context of the known safety profiles of lete-cel and pembrolizumab.

Most toxicities associated with lymphodepleting chemotherapy and lete-cel occur in the first 4 weeks of therapy. Resolution of these toxicities is generally observed by Week 4 post T-cell infusion (approximately 6 weeks after the initiation of lymphodepleting chemotherapy). Toxicities associated with pembrolizumab have variable times to onset.

When pembrolizumab is administered in combination with lete-cel, it is expected that the checkpoint blockade will activate the immune system. This could lead to enhanced antitumor activity as well as toxicity.

In the absence of a clear alternative etiology (e.g., chemotherapy and concomitant medications, disease progression, infections, etc.), AEs should be considered potentially immune-related. Immune-related AEs may include diarrhea/colitis, rash, hepatitis, GVHD, CRS, secondary pancytopenia, pneumonitis, endocrinopathies, nephritis, and any other manifestations that may indicate an immune-related phenomenon. Any clinical imaging performed to assess AEs may be collected centrally for review.

Based on review of the safety data, a decision whether to suspend treatment for an in-depth evaluation will be made collaboratively with input from the Sponsor, the Investigators, and the SRT.

Additional criteria for possible suspension of treatment/enrollment are also provided in Section 8.3.3.

8.3.1. Safety Review Team (SRT)

The SRT ensures a safety review process for the ongoing evaluation of GSK products undergoing clinical development and provides a forum for a proactive, aggregate, and holistic evaluation of the safety profile of the investigational product over the developmental lifecycle of the product, with systematic, periodic, and documented reviews.

In accordance with routine pharmacovigilance, the SRT, which will include study team members will review unblinded safety data, including clinical laboratory parameters and AEs, at appropriate intervals during the period of study conduct. Recommendations on study modification, pausing the study and/or pausing enrollment will be provided by the SRT. The roles and accountabilities, and the process for safety review and meeting frequency will be specified in the SRT charter.

8.3.1.1. Mandated Study Pause Due to GBS

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

8.3.2. Treatment Limiting Toxicities Definition

The following toxicities are considered to be treatment limiting toxicities (TLTs):

- Any ≥ Grade 4 AE (excluding events listed in this section as not considered to be TLTs)
- Grade 3 non-infectious pneumonitis

- Any other Grade 3 AE (excluding pneumonitis and events listed in Table 15 and in this section as not considered to be TLTs), that does not improve to Grade 2 within 7 days after onset despite medical management and supportive care

The following toxicities are NOT considered to be TLTs:

- Grade 3 or 4 leukopenia, neutropenia, or febrile neutropenia
- Grade 3 or 4 thrombocytopenia not associated with significant bleeding;
- Grade 3 anemia that is not aplastic
- Grade 3 laboratory abnormality determined to be not clinically significant by the Investigator
- Grade 3 or 4 fever and chills
- Grade 3 or 4 hypoalbuminemia or abnormal electrolytes that are responding to supplementation/correction
- AE related to the cancer or its progression

Any AE not listed above may be considered a TLT after consultation with the Sponsor, the Investigators, and the SRT based on the emerging safety profile.

In addition, if a participant in Arms B or C could not be administered pembrolizumab on Day 22 (Week 4 Day 1) due to an AE and the said AE has not resolved to an acceptable level by the next scheduled dosing day (Week 7 Day 1), the participant will be discontinued from treatment and the AE will be considered a TLT.

8.3.3. Treatment Limiting Toxicities for Pembrolizumab

To evaluate the safety of the combination therapy in Arms B or C, TLTs will be assessed for the 3-week period as follows:

- from Week 4 to Week 7 for participants who initiated pembrolizumab on Week 4 Day 1
- from Week 7 to Week 10 for participants who initiated pembrolizumab on Week 7 Day 1

8.3.4. Monitoring and Management of Replication-Competent Lentivirus

Replication Competent Lentivirus (RCL) is a theoretical risk associated with the use of lentiviral vectors; no RCL has ever been reported *in vivo* and/or *in vitro*. The risk is derived from the detection of replication competent retrovirus (RCR) during the use of early γ retroviral vector packaging systems which were inadequately designed to avoid recombination events between the vector and packaging components [Miller, 1990].

Updated γ retroviral packaging systems have not been associated with RCR. However, in a study with Rhesus monkeys, 3 out of 10 animals died of lymphomas at around 6 months after transplantation of vector transduced bone marrow cells contaminated with replication-competent virus [Donahue, 1992]. Therefore, RCR/L must continue to be rigorously evaluated in vector and cell lots, and in participants post infusion with any product involving a retrovirus [FDA, 2020a; FDA, 2020b; FDA, 2010].

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

Regulatory Agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a participant [FDA, 2020a; FDA, 2020b; FDA, 2010]. However, because the probability and characteristics of an RCL are unknown, no concrete plans have been put in place.

The following approaches have been discussed for participant management:

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

8.3.4.1. Testing for RCL in Clinical Studies

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

- The lentiviral vector, whereby RCL testing will be performed on vector supernatant and end of production (EOP) cells by or under the direction of the manufacturing facility responsible for manufacturing and releasing the vector.
- The T-cell product, whereby VSV-G qPCR testing will be carried out for release and biological RCL testing will also be performed.

- Participant PBMCs will be collected at time points indicated in the SoA. Once persistence of gene modified cells is below the level of detection for 2 consecutive assessments, RCL sample collection will discontinue.

  If VSV-G DNA copies are detected at any time point in the first-year post-infusion, the safety monitoring protocol will be triggered. Participant samples will continue to be tested for VSV-G DNA copies until VSV-G DNA copies are not detected for 3 consecutive annual assessments.

8.3.4.2. Safety Monitoring Results

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

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

If the biological RCL is positive, all lete-cel infusions will be paused. An action plan will be discussed with FDA and other Regulatory Authorities and experts as appropriate. Additional participants will not be treated until such time as a plan is agreed upon, completed, and reviewed.

8.3.5. Testing for Persistence of Transduced T cells and Insertional Oncogenesis

Peripheral blood mononuclear cell (PBMC) samples will be collected for monitoring persistence of gene modified cells. The samples will be tested using a DNA PCR-based method to detect the presence of the Psi gene, which is part of the lentiviral vector used to transduce T-cells. The Sponsor will notify the site once the participants' transduced T cells are below the level of detection for 2 consecutive visit assessments. Following this, RCL and persistence sample collection will discontinue.

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

If there is clonal dominance in the genetically modified T-cell population (either monoclonality or oligoclonality), the persistence of gene modified cells and integration site assessment will be repeated within 3 months on a new sample.

If the repeated analysis demonstrates: 1) persistent monoclonality, 2) evidence of insertional oncogenesis or 3) clonal expansion (an increase in percent predominance of a clone), there will be a review by GSK's SRT and Safety Governance Board to develop a monitoring plan specific to the health care risk and strategies to inform participants, investigators, FDA, and other regulators of the findings.

If the integration site analysis indicates polyclonality of the genetically modified T-cell population, then study and persistence monitoring will continue as scheduled. Integration site assessment will only be repeated if there is a sudden increase in persistence or if there is any suspicion/report of potential hematological malignancy.

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

8.3.6. Monitoring and Management for Demyelinating Neuropathy and Other Neurological Events

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

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and will be graded by the Investigator according to the NCI-CTCAE (v4.03).

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

Collection of AEs and SAE will be performed as follows:

- SAEs or AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or leading to early withdrawal will be collected in the AE section of the CRF from the time a participant signs the informed consent form to leukapheresis (Part 1 and leukapheresis). All other relevant events that begin before the start of leukapheresis but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

- After leukapheresis until the lymphodepletion, all SAEs assessed as related to study participation and other reportable safety events that could affect patient eligibility or study participation (e.g., protocol-specified intervention, including but not limited to, wash-out or discontinuation of usual therapy, diet, or a procedure) will be collected.
- From lymphodepletion to end of study (Part 3 and Part 4), all AEs and SAEs will be collected at the time points specified in the SoA (Section 1.3).
- All SAEs will be recorded and reported to the Sponsor (or designee) immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- The AESIs (Section 8.4.4) and will be reported to the Sponsor (or designee) immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3.
- All AEs or AESIs (listed in Section 8.4.4) from the time of lymphodepletion through 30 days following cessation of study treatment or end of study, whichever is later.
- All SAEs must be collected through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier.
- All pregnancies and exposure during breastfeeding, from the start of chemotherapy (lymphodepletion regimen) through the contraception period (see Section 5.3.3) must be reported by the Investigator.
- Additionally, any SAE brought to the attention of an Investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.
- AEs and SAEs occurring after the participant rolls over to the LTFU study (GSK Study 208750) will be collected and reported in the LTFU protocol database.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, including AESIs (as defined in Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4. Adverse Events of Special Interest (AESIs)

AESIs for this trial should be reported to GSK within 24 hours via e-mail to the Medical Monitor. The AESIs include:

- CRS, pneumonitis/pneumonia, GVHD, Guillain Barre syndrome (GBS) or acute inflammatory demyelinating polyneuropathy (AIDP), pancytopenia/aplastic anemia, and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grade 1 persisting beyond 24 hours or associated with concurrent CRS; or Grade 2 or higher, Treatment-related inflammatory response at tumor site(s), and Grade 4 neutropenia lasting ≥28 days (Appendix 9).
  - For pancytopenia/aplastic anemia, this will be treated as an AESI with expedited reporting within 24 hours if any of the below events occur:
    - Requiring a transfusion (e.g., platelets or red blood cells [RBC])
    - Occurs after bone marrow reconstitution following the lymphodepletion regimen
    - Any Grade 3 or 4 cytopenia following lymphodepletion lasting more than 2 weeks with G-CSF support.
  - Any Grade ≥3 CRS or GVHD, and all cases of GBS or acute inflammatory demyelinating polyneuropathy must be reported as an SAE within 24 hours.
- An overdose of pembrolizumab, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT laboratory value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase (ALP) laboratory value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

  Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow-up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Medical Monitor or designee. However, abnormalities of liver blood tests that do not meet the criteria noted above are not AESIs for this trial.

8.4.5. Reporting Criteria during Long-Term Follow-Up (Years 1 through 15)

Delayed Adverse Events:

Due to the nature of the treatment, participants are required to be followed for up to 15 years after treatment with genetically modified T-cells (lete-cel) for observation of delayed AEs according to FDA and EMA guidance [FDA, 2020a; FDA, 2020b; EMA, 2009]. Delayed AEs are defined as those events that fall into one or more of the 6 categories listed below and which occur either after disease progression or last Interventional Phase visit, whichever occurs first, and are considered related to GSK's gene modified cell therapy. Delayed AEs will be collected as part of the LTFU phase of the study or in the LTFU Study 208750, contingent upon formal transfer of participant to Study 208750:

Delayed AEs will be collected until 5 years have elapsed from last T-cell infusion, or until patient dies, withdraws consent or is deemed lost to follow-up. Delayed AEs will be recorded in the CRF if reported by the patient or investigator between years 6 – 15.

The 6 categories of delayed AEs are:

- New malignancies
- New incidence or exacerbation of a preexisting neurological disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of a hematologic disorder
- New incidence of an infection (potentially related to gene-modified cell therapy)
- Unanticipated illness or hospitalization deemed related to gene modified cell therapy

For participants who received pembrolizumab and who have an allogeneic stem cell transplant (allo-SCT) within 24 months of last dose of pembrolizumab, specific AEs (all grades, and regardless of relationship to study drug) will be collected for 18 months from the date of the transplant, to include:

- Graft-versus-host-disease
- Veno-occlusive disease
- Febrile syndrome (a steroid-requiring febrile illness without an infectious cause)
- Encephalitis

Additional medically important AEs post-allo-SCT may be reported at the investigator's discretion.

If a participant is monitored in this protocol post disease progression, s/he will only be monitored for the AEs detailed above.

A detailed description of the event should include the date of diagnosis and the nature of the diagnosis. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites. If a new malignancy is recorded in a vector target cell type, tumor cells will be evaluated for vector sequences. If the tumor is positive for vector sequences or the surrogate sample is positive for vector sequences and is confirmed in accordance to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled, and submitted within the annual report of the INDs listed on this protocol under which the participant(s) originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the participant(s) originally received their treatment. Suspected unexpected serious adverse reactions (SUSARs) deemed related to the gene modified cells will be reported to the Regulatory Agencies and shared with Investigators as necessary in the form of Investigator Notification Letters (INL).

8.4.6. Regulatory Reporting Requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.7. Pregnancy

Contraception is defined from the start of study intervention and for the period defined below, based on the study treatments received:

Study Intervention Received	**Contraception to continue from start of study intervention through longest of all intervals defined below based on all treatments received**
Fludarabine	6 months after last dose of fludarabine
Cyclophosphamide	Time after last dose of cyclophosphamide: Females – 12 months Males – 6 months

NY-ESO-1 specific T cell infusion	A minimum of 12 months after NY-ESO-1 specific T-cell infusion, 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.
Pembrolizumab	A minimum of 4 months after the last dose of pembrolizumab, if this time frame is longer than the duration of contraception required in the context of fludarabine, cyclophosphamide and NY-ESO-1 specific T cells.

The Sponsor will notify the site once the participant's persistence is below the level of detection for 2 consecutive assessments.

- Should female participant or female partner of male participant become pregnant during the contraception period, details of pregnancies need to be collected and reported as described in Section 10.4.
- If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- If appropriate, the investigator should advise fertile male participants to consider collecting and storing viable sperm prior to undergoing lymphodepletion, given that cyclophosphamide may result in partial (oligospermia) or total (azoospermia) sterility

8.4.8. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 (Appendix 3), and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

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

8.4.9. Progression of Underlying Malignancy

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

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

8.5. Treatment of Overdose

Lete-cel is administered as a single dose by trained personnel at the investigational sites in this study.

An overdose of pembrolizumab is defined as any dose of ≥1000 mg (≥5 times the indicated dose of 200 mg) Q3W. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor's Medical Monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

As described in Section 8.9.3, the pharmacokinetics (levels, expansion, persistence) of engineered T-cells will be measured and will be used to derive PK parameters. The timing of assessment is provided in the SoA (Section 1.3).

- Whole blood samples will be collected for measurement of lete-cel transduced cell quantities as specified in the SoA (Section 1.3). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The following PK parameters of lete-cel will be computed, as data permit:

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

Serum concentrations of pembrolizumab will be obtained pre and post infusion and samples for evaluation of pembrolizumab CCI [redacted] will also be collected as described in the SoA (Section 1.3).

8.7. Pharmacodynamics

Research cytokine assessments and other biomarkers measurements (see Section 8.9) may be evaluated for pharmacodynamic relationships with lete-cel administration.

CCI [redacted]

CCI

[redacted]

8.9. Biomarkers

CCI

[redacted]

CCI

[redacted]

8.9.1. Cytokine and Soluble Factors Analysis

Serum is collected at Baseline, and at each visit post lete-cel infusion, at designated timepoints within SoA, to allow for measurement of cytokines in the blood. Serum is also collected from participants with suspected CRS, with samples being taken every day for the first week and approximately every other day thereafter until symptoms are

improving or an alternative diagnosis is confirmed (Section 10.9.5). Details regarding serum collection are provided in the SRM and/or Laboratory Manual.

CCI

[redacted]

8.9.2. Tumor Biopsies

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

Screening Biopsy

Archival tissue from the most current setting may be used for the Screening biopsy if it is of good quality. If multiple archival samples are available, then the most recent archival sample should be used. If an archived biopsy of the tumor tissue is not available, then a fresh tumor tissue biopsy is required for screening. The tumor biopsy will be screened at the central reference laboratory for expression of tumor antigens, NY-ESO-1 and/or, if tested, LAGE-1a. In the event that the tumor tissue samples submitted for antigen expression is of insufficient quantity or quality to conduct the testing and determine tumor antigen expression profile, additional tissue samples(s) may be submitted to the central laboratory.

Tumor samples must meet the following criteria:

a. Formalin-fixed paraffin embedded (FFPE) tumor specimens in paraffin blocks are preferred. A minimum of 20 (or more) unstained slides (5-micron serial fresh cut) is required as an alternative. Patients with fewer than 20 unstained slides may still be considered for screening following discussion with Medical Monitor. The sites internal pathologist should confirm >20% tumor content and >1.0 mm^3 tumor volume prior to shipment.

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. Tumor tissue from bone metastasis is not advised.

d. Tissue should be obtained from 1 year of consent and be of good quality on the basis of total and viable tumor unless discussed with Medical Monitor.

Baseline Biopsy

A baseline tumor biopsy obtained prior to initiating lymphodepleting chemotherapy will be mandatory for all participants and should meet the following criteria:

a. 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

b. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavages are not acceptable. Tumor tissue from bone metastasis is not advised.

The tumor sample needs to be either a freshly collected tumor biopsy or a tumor biopsy taken after completion of the participant's last line of therapy. In cases when such a biopsy is clinically unsafe to perform, archival (meaning obtained at earlier times) tumor biopsies, preferably within 90 days prior to initiating lymphodepleting chemotherapy, may be accepted at the discretion of the Medical Monitor (or designee). Tumor tissue should be taken from non-target lesions. If this is not feasible, then a fresh biopsy of the target lesion may be considered upon consultation with the Sponsor's Medical Monitor (or designee).

Post-T-Cell Infusion Biopsies

A mandatory tumor biopsy in non-target lesions will be performed a) 4 weeks after lete-cel infusion and b) when the participant experiences progressive disease, unless clinically unsafe to do so. If this is not feasible, then a fresh biopsy of the target lesion may be considered upon consultation with the Sponsor's Medical Monitor (or designee).

When possible, the same lesion(s) should be biopsied at both Screening and subsequent time points. The apparent clinical or scan status of the lesion(s) biopsied should be documented at the time (e.g., decreased, stable, increased size or activity).

Additional details regarding tumor biopsy collection and processing are provided in the SRM and/or Laboratory Manual.

Clinically obtained pleural effusion/ascites samples have been shown to be a rich source of tumor cells, tumor infiltrating leukocytes and soluble factors, changes in which have been reported to correlate with disease prognosis and therapy response. CCI

[redacted]

CCI

[redacted]

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

8.9.3. Transgene persistence for PK assessment

Lete-cel T-cell pharmacokinetics in the peripheral blood will be measured in the participants to establish the relationship between persistence and response to lete-cel. Persistence is also monitored as a long-term safety measure.

The following methodology will be used to measure the cells: Quantitation of transduced cells by PCR of transgene from DNA extracted from frozen PBMCs.

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

8.10. Request for Autopsy for Death Following Administration of Gene Transfer Agents

In accordance with FDA and EMA guidance [FDA, 2020a; EMA, 2009], all participants enrolled in this trial are asked to consider pre-authorizing (in advance) an autopsy in case of death, and autopsies will be requested of the families for all participants who die during participation in studies after administration of gene transfer agents. To assure compliance, guidelines for performing an autopsy are provided in the SRM and/or Laboratory Manual.

CCI [redacted]

CCI

[redacted]

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is a Phase 1b/2a study focused on the safety, tolerability, clinical activity, and whether HLA and antigen expression biomarkers can identify a population of participants with advanced NSCLC that could benefit from lete-cel administered alone or in combination with pembrolizumab.

No formal statistical hypotheses are being tested in this study.

9.2. Sample Size Determination

The sample size for each arm was determined using a Bayesian predictive adaptive design that allows the study to be monitored more frequently while maintaining the desired Type I error and power. The sample size is based on testing the hypothesis for each arm separately and not for a comparison between arms. For all three arms, clinical response will be defined as investigator-assessed ORR per RECIST v1.1. An interim analysis after the 10th participant becomes evaluable will be employed for Arms A, B, and C, respectively.

Participants with NSCLC lacking actionable genetic aberrations will be assigned to Arm A and Arm B such that approximately 15 participants receive T-cell infusion within the target dose range (lete-cel) in Arm A and approximately 15 participants receive T-cell infusion within the target dose range and pembrolizumab in Arm B. Participants with NSCLC with actionable genetic aberrations will be assigned to Arm C such that approximately 15 participants receive T-cell infusion and pembrolizumab. Assuming around 15% of the participants enrolled will discontinue from the study prior to lete-cel infusion, approximately 18 subjects will be enrolled in each arm to ensure approximately 15 evaluable participants will receive T-cell infusion within the target dose range. Enrollment will proceed continuously with no scheduled enrollment pause while

conducting the interim analysis. Upon completion of the interim analysis, this protocol may be amended to allow for expansion.

Analyses will be conducted for Arms A, B, and C independently. An end of study threshold is defined such that meeting this threshold may warrant continuing development in the population of interest. For each arm, Bayesian statistics will be employed to calculate the predictive probability of meeting the end of study threshold at the interim analysis (after the 10^{th} enrolled participant per arm has received T-cell infusion (modified Intent-to-Treat [mITT] population) and has completed at least 2 post-baseline disease assessments since infusion or discontinued earlier) given the responses that have already been observed assuming a beta prior for the binomially distributed data. A weak prior of beta (0.02, 0.08) is used, which is equivalent to the information present in 0.1 participant.

At the interim analysis for each arm, further enrollment into the arm is recommended to be stopped if the predictive probability of meeting the threshold at the final analysis is less than 2.8%. Here, this threshold is defined as the posterior probability that the ORR is greater than 10% at the end of the arm is larger than 95%. This predictive probability aligns with observing at least 2 responders out of 10 evaluable participants, and if not met, serves as strong statistical evidence to stop further development of the treatment for the target population.

If 4 responses out of 15 evaluable participants are observed at the final analysis, this will serve as evidence in favor of further development in this arm. Operating characteristics for a range of true population ORR are given in Table 19. The probability of reaching the continuing development criteria at the final analysis, given a true ORR of 30% is 68.1%. The inference from the Bayesian predictive probabilities of clinical activity in participants in each treatment arm is intended to drive decision making. Actual decisions will depend on the totality of the data including clinical activity, safety, PK, and biomarker data.

Table 19 Operating Characteristics for Interim and Final Analyses for Arms A, B, and C

True ORR	Probability of passing futility at interim (n=10)	Probability of reaching end of study threshold at final analysis (n=15)
10%	0.265	0.054
20%	0.625	0.334
30%	0.850	0.681
40%	0.953	0.896
50%	0.988	0.976

9.3. Populations for Analyses

For analysis purposes, the following populations are defined:

Screened Population: All participants who signed an ICF to participate in the study.

Enrolled Population: All participants who started leukapheresis procedure.

Intent-to-treat (ITT) Population: All participants who started leukapheresis procedure.

Modified ITT (mITT) Population: All participants who received lete-cel infusion. This population will be the primary population for the efficacy analysis.

All Evaluable Population: Defined as the study population used for decision-making at the interim analyses. This population will be the primary population for interim efficacy analyses and include participants in the mITT population with at least 2 post-baseline radiological disease assessments or have progressed, died, or permanently withdrawn from the study if in Arm A or have progressed, died or permanently withdrawn from pembrolizumab if in Arm B or C. Further details are provided in the Reporting and Analysis Plan (RAP).

Safety Population: The ITT Population will be used for all safety analyses.

Additional analysis populations may be defined in the RAP.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

Table 20 Efficacy Endpoints and Statistical Methods

Endpoint	Statistical Analysis Methods
Primary	Clinical response: ORR (according to RECIST v1.1)
Secondary	PFS DCR DoR TTR
Exploratory	Will be reported in the RAP

Abbreviations: DCR = disease control rate; DoR = duration of response; ORR = overall response rate; PFS = progression-free survival; RAP = Reporting and Analysis Plan; TTR = time to response.

9.4.1.1. Primary Efficacy Analysis

The primary efficacy endpoint is the ORR, defined as the percentage of participants (mITT Population) with a CR or PR as determined by investigator assessment and confirmed by repeat assessment at least 4 weeks after the initial documentationas per RECIST v1.1.

Bayesian predictive adaptive design (Lee, 2008) will be used to investigate the clinical activity in each treatment arm.

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

The observed confirmed ORR will be reported at the interim and final analyses for each arm. The estimates along with 95% Clopper-Pearson exact confidence interval (CI) will be provided.

9.4.1.2. Secondary Efficacy Analysis

DCR is defined as the percentage of participants with a confirmed CR, PR, or stable disease (SD) for at least 6 months as per RECIST v1.1.

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

PFS is defined as the time from the date of T-cell (lete-cel) infusion until the earliest date of disease progression as assessed by the Investigator per RECIST v1.1, or death due to any cause. For the analysis of PFS, if the participant received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g., assessment when visit level response was CR, PR, or SD) prior to the initiation of therapy. Progressive disease will also be defined per RECIST v1.1 criteria. Otherwise, if the participant does not have a documented date of event, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. PFS will be summarized by arm using Kaplan-Meier quantile estimates along with 2-sided 95% CIs estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982] at the time of final analysis, if data warrant.

DoR is defined as, in the subset of participants who show a confirmed CR or PR, the time from first documented evidence of CR or PR until the first documented sign of disease progression or death. DoR will be summarized descriptively for each arm, if data warrant, using Kaplan-Meier medians and quartiles. Details on rules for censoring will be provided in the RAP.

Time to response (TTR), defined as the time from the date of T-cell (lete-cel) infusion to the first documented evidence of response (PR or better) in the subset of participants who achieved a confirmed PR or CR as assessed by the Investigator.

9.4.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

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

9.4.2.1. Adverse Events

AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and will be graded by the Investigator according to the NCI-CTCAE (v4.03).

Events will be summarized by frequency and proportion of total participants and by SOC and preferred term (PT). Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment and dose modification. In addition, AEs, if listed in the NCI-CTCAE v4.03, will be summarized by the maximum grade. AESIs will be further outlined in the RAP.

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

9.4.2.2. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4.03. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Further details will be provided in the RAP.

9.4.2.3. Other Safety Measures

Data for vital signs, ECGs, and left ventricular function (ECHO and MUGA) will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the RAP.

9.4.3. Other Analyses

Pharmacokinetics (lete-cel persistence and pembrolizumab concentrations), pharmacodynamic, and biomarker and other exploratory analyses details will be described in the RAP.

9.5. Interim Analyses

For the primary purpose of informing future lete-cel development, separate interim analyses are planned for each arm after at least 10 evaluable participants are available in that arm. Evaluable participants are defined as participants who received a T-cell infusion and have either progressed, withdrawn from the study treatment, were lost to follow-up, or are ongoing and have completed at least two post-treatment disease assessments. If enrollment is still open at the time of the interim analysis, enrollment into a treatment arm may be stopped early for toxicity or lack of efficacy (futility) based on the results of an interim analysis.

Futility interim analysis decision guidelines for each arm, specifying the number of participants with a confirmed response needed for continuing enrollment or stopping for futility is presented in Table 21.

Table 21 Decision-Making Criteria for Futility for Arms A, B, and C at the Interim Analysis Conducted with 10 Evaluable Participants/Arm

Arm (N=10/Arm)	Stop Enrollment for Futility if the Number of Confirmed Responses is Less Than or Equal to this Number	Probability of Continuing Enrollment under H0 (10%)	Probability of Continuing Enrollment under Ha (30%)
Arm A or B or C	1	0.2639	0.8507

Based on interim analysis results, enrollment for all treatment arms (Arm A, B, or C) may be stopped due to futility if ≤1 confirmed response is observed in the first 10 evaluable participants within the arm, i.e., the predictive probability that rejecting H0 at end of study is small (e.g., less than 2.8% chance to have at least 4 confirmed responders out of 15 participants who received T-cell infusion in the treatment arm). The above criteria are intended as guidelines. Final decisions with respect to study conduct, including pausing enrollment, will be based on a comprehensive review of the totality of the data including safety, DCR, DoR, CR rate, and PFS as warranted by the data.

All planned interim analyses will be described in greater detail in the RAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor (or designee) electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor (or designee) is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

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

10.1.8. Study and Site Closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or

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

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 22 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy Testing: Refer to Section 1.3 for SoA.
    - Pregnancy testing (urine or serum as required by local regulations) should be conducted as indicated in the SoA (Section 1.3).
    - Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 22 Protocol-Required Safety Laboratory Assessments

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

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein- Barr virus; GFR = glomerular filtration rate; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; eCRF = electronic case report form; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; HTLV = human T-lymphotropic virus; IgG = immunoglobulin G; INR = international normalized ratio; IRB/IEC = Institutional Review Board/Independent Ethics Committee; LAGE-1a = cancer testis antigen 2; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; NT-proBNP = N-terminal pro B-type natriuretic peptide; NY-ESO-1 = New York esophageal squamous cell carcinoma 1; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cells; SAE = serious adverse event; T4 = thyroxine; TSH = thyroid stimulating hormone; ULN = upper limit of normal; WBC = white blood cells.

a. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Table 15. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

a. Either BUN or UREA tests are acceptable

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

Note: All study-required laboratory assessments will be performed by a local laboratory, with the exception of biomarkers HLA –A2:01, A2:05, or A2:06 and NY-ESO-1/LAGE-1a. The results of each test must be entered into the eCRF.

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

10.3.1. Definition of AE

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

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

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

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

10.3.2. Definition of SAE

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

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

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

10.3.3. Definition of Cardiovascular Events

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

10.3.4. Recording and Follow-Up of AE and SAE

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

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

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03 as in the SRM) except for the following:

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

Assessment of Causality

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

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

Follow-up of AE and SAE

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

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

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

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

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP):

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Table 23 Contraceptives Allowed During the Study

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormonal contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is participating in this study. This applies only to male participants who receive study treatment.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the Investigator will be reported to GSK as described in Appendix 3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating will discontinue study intervention and be monitored into the LTFU protocol (GSK Study 208750) or to Part 5 of this study (if not yet enrolled in the LTFU study).

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to lete-cel or lete-cel in combination with pembrolizumab, or advanced/recurrent NSCLC and related diseases. They may also be used to develop tests/assays including diagnostic tests related to lete-cel alone and/or in combination with pembrolizumab, or study treatments of this drug class, and advanced or recurrent NSCLC. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome as appropriate.
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analyzed by using appropriate descriptive and/or statistical analysis methods. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to lete-cel alone and/or in combination with pembrolizumab or study treatments of this class. The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on lete-cel alone and/or in combination with pembrolizumab or study treatments of this class or NSCLC and related diseases continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

10.5.1. Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the participant does not meet the entry criteria for participation in the study, then the Investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance, a sample destruction form will not be available to include in the site files.

10.5.2. Germline Control

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

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

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

10.6. Appendix 6: Liver Safety

See Table 11 for hepatic parameter requirements for study inclusion.

See Section 7.1.1.1 for liver event monitoring criteria.

See Section 7.1.1.1 for study intervention restart and re-challenge criteria

See Table 16 for pembrolizumab dose modification and treatment guidelines.

10.7. Appendix 7: Country-Specific Requirements

Not applicable.

10.8. Appendix 8: Abbreviations and Trademarks

List of Abbreviations

Abbreviation	Definition or Explanation
ABW	Adjusted body weight
ACT	Adoptive T-cell therapy
CCI [redacted]	
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immune deficiency syndrome
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATG	Antithymocyte globulin
ATTACK	Adoptive engineered T-cell targeting to activate cancer killing
AUC(0-t)	Area under the concentration/persistence time curve from 0 to time t
BCG	Bacillus Calmette–Guérin
BRAF	B-Raf
BSA	Body surface area
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T-cell
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CD28	Cluster of differentiation 28
CD3	Cluster of differentiation 3
CD3ζ	CD3 zeta
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
cfDNA	Cell-free DNA
CFR	Code of Federal Regulations (US)
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic kidney disease epidemiology collaboration
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum observed concentration/persistence
CMV	Cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated standards of reporting trials
CPD	Confirmed progressive disease (iCPD = CPD based on CCI [redacted])
CPK	Creatine phosphokinase
CR	Complete response (iCR = CR based on iRECIST)

Abbreviation	Definition or Explanation
CrCl	Calculated creatinine clearance
CRES	CAR T-cell related encephalopathy syndrome
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical Trial Assay
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic t-lymphocyte-associated protein 4
CV	Cardiovascular
DCR	Disease control rate CCI [redacted]
DLCO	Pulmonary diffusing capacity for carbon monoxide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DoR	Duration of response CCI [redacted]
DRESS	Drug rash with eosinophilia and systemic symptoms
DSUR	Drug Safety Update Report
EBV	Epstein-Barr virus
ECG	Electrocardiogram(s)
ECHO	Echocardiography
eCOA	Electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMG	Electromyography
EOP	End of production
EoT	End of treatment
ES	Encephalopathy syndrome
EVI1	Ecotropic viral integration site 1
FACT-GP5	Functional Assessment of Cancer Therapy – General Population
FDA	Food and Drug Administration
FDG PET	Fluorodeoxyglucose positron emission tomography
FEV1	Forced expiratory volume in 1 second
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GBS	Guillain-Barré Syndrome
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice

Abbreviation	Definition or Explanation
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony stimulating factor
GSK	GlaxoSmithKline
GBS	Guillain-Barré Syndrome
GVHD	Graft versus host disease
Gy	Gray (unit of absorbed dose of radiation)
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HRT	Hormone replacement therapy
CCI [redacted]	
HTLV	Human T-lymphotropic virus
IB	Investigator's brochure
IBW	Ideal body weight
ICE	Immune Effector Cell-Associated Encephalopathy
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICF	Informed consent form
ICH	International Council for Harmonisation
ICP	Intracranial pressure
IEC	Independent ethics committee
IFN	Interferon
CCI [redacted]	
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgV	Immunoglobulin variable–type
IL	Interleukin
IND	Investigational New Drug
INL	Investigator notification letter
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
CCI [redacted]	
irAE	Immune-related adverse event
IRT	Interactive response technology
ITT	Intent to treat
IUD	Intrauterine device

Abbreviation	Definition or Explanation
IUS	Intrauterine system
IV	Intravenous
IVD	*in vitro* companion diagnostic device
LAGE-1a	Cancer testis antigen 2
LAM	Lactational amenorrhea method
LDH	Lactate dehydrogenase
LFT	Liver function test
LMO2	LIM domain only 2
LPS	Lipopolysaccharide
LTFU	Long-term follow-up
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSDS	Material Safety Data Sheet
MUGA	Multigated acquisition scan
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tropomyosin-related kinase
NY-ESO-1	New York esophageal squamous cell carcinoma 1
NYHA	New York Heart Association
ORR	Overall response rate CCI [redacted]
OS	Overall survival
OTC	Over-the-counter
PBL	Pembrolizumab baseline
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically-based pharmacokinetic(s)
PCP	Pneumocystis carinii pneumonia
PCR	Polymerase chain reaction
PD	Progressive disease CCI [redacted]
PD-1	Programmed death protein 1
PD-L1	Programmed death protein 1 ligand
PD-L2	Programmed death protein 2 ligand
Pdcd1	Gene encoding PD-1
PFS	Progression-free survival CCI [redacted]
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
PKCθ	Protein kinase C-theta
PMBC	Peripheral blood mononuclear cell

Abbreviation	Definition or Explanation
PR	Partial Response CCI [redacted]
PRO	Patient-reported outcomes
PRO-CTCAE	Patient-reported outcome version of the common term criteria for adverse events
PS	Performance status
PT	Prothrombin time
PV	Pharmacovigilance
PW	Pembrolizumab Week
Q#W	Every # week(s)
QLQ	Quality of life questionnaire
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
QTc	Corrected QT interval duration
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and analysis plan
RBC	Red blood cell
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RECIST	Response Evaluation Criteria in Solid Tumors
CCI [redacted]	
ROS1	c-ros oncogene 1
RT	Reverse transcriptase
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SCID-X1	X-linked severe combined immunodeficiency
SD	Stable disease CCI [redacted] or standard deviation (context dependent)
SHP-1	Src homology 2 containing phosphatase 1
SHP-2	Src homology 2 containing phosphatase 2
SJS	Stevens-Johnson Syndrome
SoA	Schedule of activities
SoC	Standard of care
SOP	Standard operating procedure
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reactions
T1DM	Type 1 diabetes mellitus
T4	Thyroxine
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TCR Valpha	TCR alpha chain variable region
TCR Vbeta	TCR beta chain variable region

Abbreviation	Definition or Explanation
TEAE	Treatment-emergent adverse event
TEN	Toxic Epidermal Necrolysis
TGF	Transforming growth factor
CCI [redacted]	
TKI	Tyrosine kinase inhibitor
TLC	Total lung capacity
TLT	Treatment limiting toxicity
Tmax	Time to Cmax
CCI [redacted]	
TMDD	Target-mediated drug disposition
TNF	Tumor necrosis factor
CCI [redacted]	
TPS	Tumor proportion score
T-regs	Regulatory T-cells
TSH	Thyroid stimulating hormone
TTR	Time to response CCI [redacted]
UPD	Unconfirmed progressive disease CCI [redacted]
ULN	Upper limit of normal
V20	Percentage of normal lung receiving at least 20 Gy during radiotherapy
VSV-G	Vesicular Stomatitis Virus G protein
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WT	Wild-type
X-CGD	X linked chronic granulomatous disease
ZAP70	Zeta-chain-associated protein kinase

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
KEYTRUDA

10.9. Appendix 9: Supportive Care Guidance

It is recommended that a specialist with experience in the administration of hematopoietic stem cell transplant and/or other cell and gene therapy be involved in the care of study participants. During lymphodepletion, supportive care should be provided to participants as per local institutional guidelines, based on established standards.

All participants must be hospitalized on the day of T-cell (lete-cel) infusion (Day 1) and may be in the hospital for follow-up care until Day 3 as clinically indicated. Longer hospitalization is allowed if clinically needed. Staff treating trial participants should be experienced in acute post-transplant care and the management of associated toxicities (e.g., cytopenias, CRS, autologous GVHD).

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

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

10.9.1. T-cell Infusion Symptom Management

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

- Fever, chills, headache and temperature elevations will be managed with acetaminophen. It is recommended that all participants who develop fever or chills have a blood culture drawn.
- Nausea and vomiting may be treated with a non-steroidal anti-emetic of choice.
- Hypotension will initially be managed by intravenous fluid administration and further measures as dictated by standard medical practice.
- Hypoxemia will initially be managed with supplemental oxygen and further measures as dictated by standard medical practice.

10.9.2. Infection

Additional measures to treat and prevent infection are outlined below. In particular, fever and neutropenia should be aggressively managed as well as preemptive influenza therapy and other standard therapies for immunocompromised hosts, in accordance with institutional guidelines. For participants with indwelling central lines, consider increased surveillance to monitor for catheter-associated infections.

10.9.2.1. Pneumocystis carinii Pneumonia (PCP)

Participants should receive prophylaxis against PCP with drug, dose and duration according to institutional guidelines. Single strength trimethoprim sulfamethoxazole

daily is the recommended first-line agent, starting at Day 28 post T-cell infusion for one year. Other regimens, including atovaquone (1500 mg daily with food) or aerosolized pentamidine (300 mg every 4 weeks) are also acceptable (e.g., if sulfonamide allergy).

10.9.2.2. Herpes Simplex and Varicella Zoster

All participants should receive prophylaxis with acyclovir (800 mg twice daily) or valacyclovir (500 mg twice daily) for 1 year, or in accordance with institutional guidelines.

10.9.2.3. Cytomegalovirus

All participants will be screened for CMV IgG seropositivity at study entry and baseline. If CMV viremia is detected at baseline, treatment should be initiated with evidence of viral clearance prior to lymphodepleting chemotherapy. All CMV IgG seropositive participants will continue to be monitored as shown in Section 1.3 for CMV viremia by CMV DNA PCR until 60 days post infusion of lete-cel. In the event CMV viremia is observed, an infectious diseases specialist should be consulted and treatment initiated if necessary according to institutional practice. Recommended regimens include ganciclovir-based therapy if absolute neutrophil count (ANC) ≥1000, and foscarnet if ANC <1000.

If a participant experiences prolonged or secondary pancytopenia or lymphopenia, additional monitoring for viral reactivation should be considered and treatment for viral infection initiated if necessary. A strategy for management of pancytopenia or bone marrow failure is described in Section 10.9.7.

10.9.2.4. Hepatitis B Prophylaxis

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

10.9.2.5. Syphilis

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

10.9.2.6. Other Anti-Microbial Prophylaxis/Treatment

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

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

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

If a participant requires anti-microbial treatment associated with risk of cardiac toxicity, consider close monitoring of cardiac function (Section 8.2.3).

10.9.3. Hematologic and Blood Product Support

Blood product support should be provided to maintain:

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

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

See AABB (formerly American Association of Blood Banks) Guideline on platelet transfusion (Kaufman, 2015).

10.9.3.1. Irradiated Blood Product

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

10.9.3.2. CMV Screened Blood Products

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

10.9.4. Management of Autoimmunity

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

10.9.5. Management of Cytokine Release Syndrome

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

CRS caused a rapid rise in serum cytokine levels under conditions of immune activation and although cytokines will be assayed serially throughout the study, results of the assays will not be available in real time; therefore, CRS should be graded and managed with supportive and immunosuppressive interventions according to the severity of symptoms [Lee, 2019]. CRS grading will include Fever, Hypoxia and Hypotension. Organ toxicities associated with CRS will be graded according to NCI-CTCAE v5.0 and do not influence CRS grading [Lee, 2019].

Table 24 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below, in alignment with (the Society for Immunotherapy of Cancer SITC) guidelines [Maus, 2020] and should be followed in conjunction with any local guidelines, where available.

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

If CRS is suspected, in addition to assessment for infection, per the Schedule of Activities (Section 1.3), the following tests should be conducted **every day for the first week** and approximately **every other day thereafter** until symptoms are improving or an alternative diagnosis is confirmed:

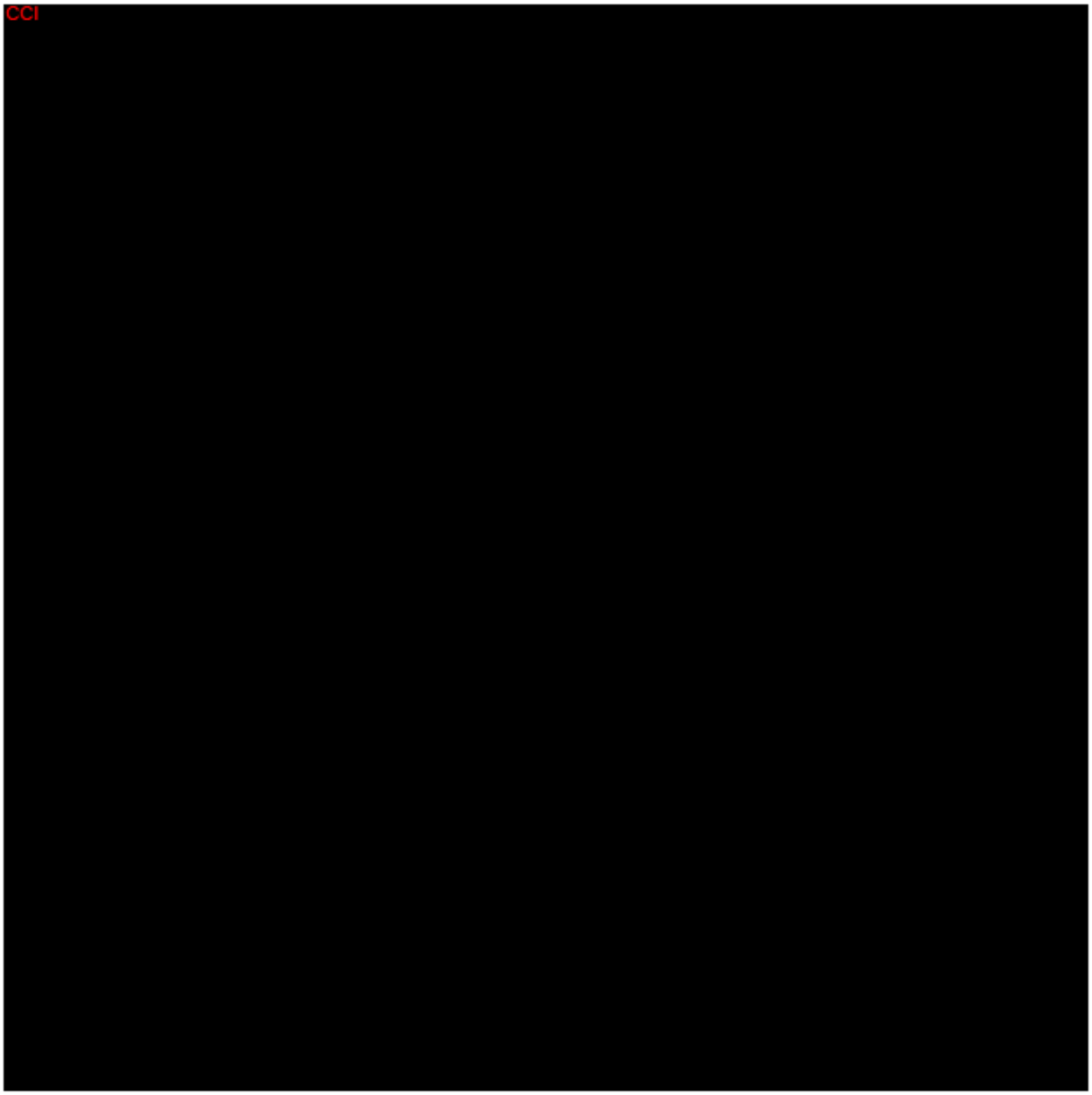
- Local tests:
  - chemistry, hematology, ferritin and coagulation, as well as C-reactive protein (CRP) labs;
- Central tests:
  - Cytokine-profiling as described in Section 8.9.1.

If CRS is suspected, participants deemed to have significant cardiovascular risk factors (per Section 8.2.3) should be considered for earlier intervention with tocilizumab and/or steroids at the onset of CRS.

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

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

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



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

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

Side effects attributed to chronic use of tocilizumab in rheumatologic disease include elevated transaminases, thrombocytopenia, elevated cholesterol and low-density lipoproteins, and neutropenia and increased infections; however, acute infusion toxicities have not been reported in CRS use [Lee, 2014; Lee, 2019].

Per SITC 2020 guidelines:

Participants unresponsive to tocilizumab or experiencing severe neurological symptoms (e.g., confusion, delirium, seizure, etc.) may require treatment with steroids. Lee et al [Lee, 2014; Lee, 2019] recommend steroids as second-line therapy for CRS as the response to tocilizumab may be more rapid and owing to the potential of steroids to attenuate the anti-tumor effects of the ACT. However, in participants with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability or other life-threatening symptomatology, consideration may be given to the use of corticosteroids as a preferred first-line immunosuppressive therapy. High doses (e.g., 2 mg/kg/day prednisone equivalent) may be required.

If CRS does not improve after one dose of tocilizumab, then steroids should be administered with a second dose tocilizumab (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 0.5 mg/kg up to 10 mg/dose). If CRS does not improve after 2 doses of

tocilizumab (and steroids), third-line agents have also been described previously, including other anti-IL6 receptor antibodies such as siltuximab with or without corticosteroids [Lee, 2014; Chen, 2016], or other anticytokine-directed therapy [Frey, 2015] such as the IL-1 receptor agonist anakinra. If steroids are used in the management of CRS, a rapid taper should be used once symptoms begin to improve [Maus, 2020].

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

Assessment and management of neurological signs and symptoms associated with CRS should include consideration of concurrent occurrence of Immune-effector cell-associated neurotoxicity syndrome (ICANS). See Section 10.9.8 for further details.

10.9.6. Management of Graft-versus-Host Disease (GVHD)

Autologous GVHD has been described in association with adoptive transfer of ex-vivo expanded/co-stimulated autologous T-cells [Raje, 2019; Rapoport , 2009] as well as infusion of T-cells with engineered specificity for NY-ESO-1 and LAGE-1a [Garfall, 2013], following high-dose chemotherapy and autologous stem cell transplant (ASCT) in participants with multiple myeloma. There is the potential for participants who receive lymphodepleting therapy followed by engineered autologous T-cell (lete-cel) infusion to experience GVHD and/or autoimmune GVHD-like symptomatology. Autologous GVHD is typically milder than classic (allogeneic) GVHD [Kline, 2008], and is usually manageable with treatment. However, severe cases (including fatalities) have been reported [Fidler, 2012]. There are no published guidelines for the management of autologous GVHD. However, lessons can be drawn from published case reports and guidelines for the diagnosis and management of acute GVHD following allogeneic transplant [Dignan, 2012].

10.9.6.1. Diagnosis of GVHD

The diagnosis of GVHD is predominantly based on clinical findings and is often one of exclusion (Table 25). Many of these symptoms can also occur in the setting of the preparative regimen, high dose cyclophosphamide as well as with CRS. Any of these conditions including GVHD can be associated with fever. The skin is the most commonly involved organ, followed by the gastrointestinal (GI) tract and liver. A constellation of symptoms involving these organ systems may be helpful in establishing the diagnosis of GVHD. Diarrhea, rash, fever, and pancytopenia are common toxicities in the lete-cel program. Mild (Grade 1 or 2) transient transaminitis without cholestasis has been observed.

Table 25 Overview of Clinical Findings/Symptoms of GVHD

Organ	Findings/Symptoms	Differential Diagnosis	Histopathology
Skin	Maculopapular rash involving the neck and shoulders as well as the	Drug reactions, viral exanthems, CRS, and effects of chemotherapy or radiation	Apoptosis at base of epidermal rete pegs, dyskeratosis, exocytosis of lymphocytes,

	palms and soles that spreads to include the rest of the body.		satellite lymphocytes adjacent to dyskeratotic epidermal keratinocytes and perivascular lymphocytic infiltration in the dermis.
GI	Secretory diarrhea is most common but nausea, vomiting, anorexia, weight loss and abdominal pain can also occur. Diarrhea can be copious. Bleeding may result from mucosal ulceration and ileus may ensue.	Side effects of chemotherapy or other drugs and infection of the GI tract	Patchy ulcerations, apoptotic bodies at crypt bases, crypt ulceration and flattening of surface epithelium
Liver	Cholestatic pattern of liver injury including elevated conjugated bilirubin, alkaline phosphatase and GGT. Participants may present with jaundice, with pruritis in more severe cases.	Veno-occlusive disease of the liver, viral infections, drug toxicity and sepsis.	Endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis and bile-duct destruction.

Abbreviations: CRS = cytokine release syndrome; GI = gastrointestinal; GGT = gamma-glutamyl transferase; GVHD = graft vs host disease.

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

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

Bone marrow suppression is also a feature of transfusion-related GVHD. To minimize the possibility of transfusion-related GVHD, refer to Section 10.9.3.1 for guidance on irradiated blood products.

10.9.6.2. Grading of GVHD

Grading of acute GVHD is based on the stage of dermal, gastrointestinal, and hepatic involvement as described in Table 27. Careful measurement of stool volume and assessment of percentage of body area covered by rash are important for proper grading and treatment.

CCI

[redacted]

With the addition of assessment of functional impairment, grading can be determined using Table 27 [Glucksberg, 1974].

CCI

10.9.6.3. Management of GVHD

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

If GVHD is suspected:

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

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

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

General guidelines for first-line treatment based on GVHD grade are provided in Table 28, and should be considered in conjunction with input from the consulting physician with bone marrow transplant expertise.

Table 28 Management Guidelines for GVHD

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

Abbreviations: GI = gastrointestinal; GVHD = graft vs host disease.

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

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

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

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

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

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

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

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

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

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

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

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

initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

Refer to Section 10.9.6 regarding bone marrow suppression as a feature of GVHD.

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

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

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

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. ICANS may occur with other cancer immunotherapies, including TCRs. Cancer patients may also be at risk for ICANS symptoms due to other causes ranging from mild to moderate somnolence and confusion as a result of sedating medications to seizures in relation to brain metastases. The possible contribution of other medications, underlying disease, and/or co-morbidities should be evaluated when considering a diagnosis of ICANS in relation to T-cell therapy.

10.9.8.1. Grading of ICANS

Lee et al [Lee, 2019] have developed a new grading system for ICANS which incorporates the use of a modified version of the CARTOX 10-point neurological assessment (CARTOX−10) tool, termed Immune Effector Cell-Associated Encephalopathy (ICE) score. Points are assigned for each of the tasks in Table 29, which are performed correctly. CCI [redacted] is defined by an overall score of 10.

The ICE should be used to monitor all participants for ICANS. The ICE score is used in grading of ICANS as presented in Table 30.

Table 29 Immune Effector Cell-Associated Encephalopathy (ICE)-Tool

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

Abbreviation: ICE = Immune Effector Cell-Associated Encephalopathy; ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome.
Scoring: 10, no impairment; 7-9; Grade 1 ICANS; 3-6, Grade 2 ICANS; 0-2, Grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS

CCI

CCI [redacted]

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

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

ICE should be measured on the day of lete-cel infusion prior to receiving treatment and then at least through Day 8 according to the schedule of activities. Participants with known brain metastases should be monitored at least twice per day for the first 5 days following lete-cel infusion. If a participant is found to have ICANS, the ICE should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

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

The recommended management of ICANS should be based on toxicity grade. Table 31 provides guidance on the management of ICANS, and should be implemented in accordance with institutional guidelines.

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

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

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

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

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

Table 31 Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

ICANS Grade	Treatment
1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV or enteral tube if swallowing is impaired • Avoid medications that cause central nervous system depression • Evaluate for other contributing causes and treat accordingly • Neurology consultation including fundoscopic exam to assess for papilloedema • MRI of the brain with and without contrast (CT scan of the brain if MRI is not feasible). Further testing if indicated and appropriate such as diagnostic lumbar puncture with measurement of opening pressure if increased intracranial pressure is suspected (as diagnosed by a neurologist), or MRI of the spine if the participant has focal peripheral neurological deficits • Consider levetiracetam therapy and EEG if seizure activity is suspected • Consider anti-IL-6 therapy if associated with concurrent CRS. Tocilizumab[1] may worsen neurotoxicity. Management of neurotoxicity may take precedence over the management of low-grade CRS, but this does not apply to high-grade CRS. Alternative IL-6 blockade may be considered (e.g. siltuximab) or the IL-1 antagonist, anakinra.
2	• As described for **Grade 1 PLUS** • Consider ICU transfer • Consider corticosteroids[2]
3	• As described for **Grade 2 PLUS** • ICU transfer is recommended • Corticosteroids are recommended • Consider repeat neuroimaging (CT or MRI) every 2 to 3 days if participant has persistent Grade ≥3 ICANS
4	• As described for **Grade 3 PLUS** • Consider neurosurgical consultation for participants with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection

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

1. Please refer to Section 10.9.5 for management of concurrent CRS.
2. Consider dexamethasone 10 mg IV every 6 h (≤ Grade 3 ICANS), or methylprednisolone 1000 mg IV every 24 h for 3 days (Grade 4 ICANS), if refractory to anti-IL-6 therapy, or for ICANS without concurrent CRS; once initiated continue corticosteroids for at least two doses until improvement to Grade 1 ICANS and then taper.

CCI

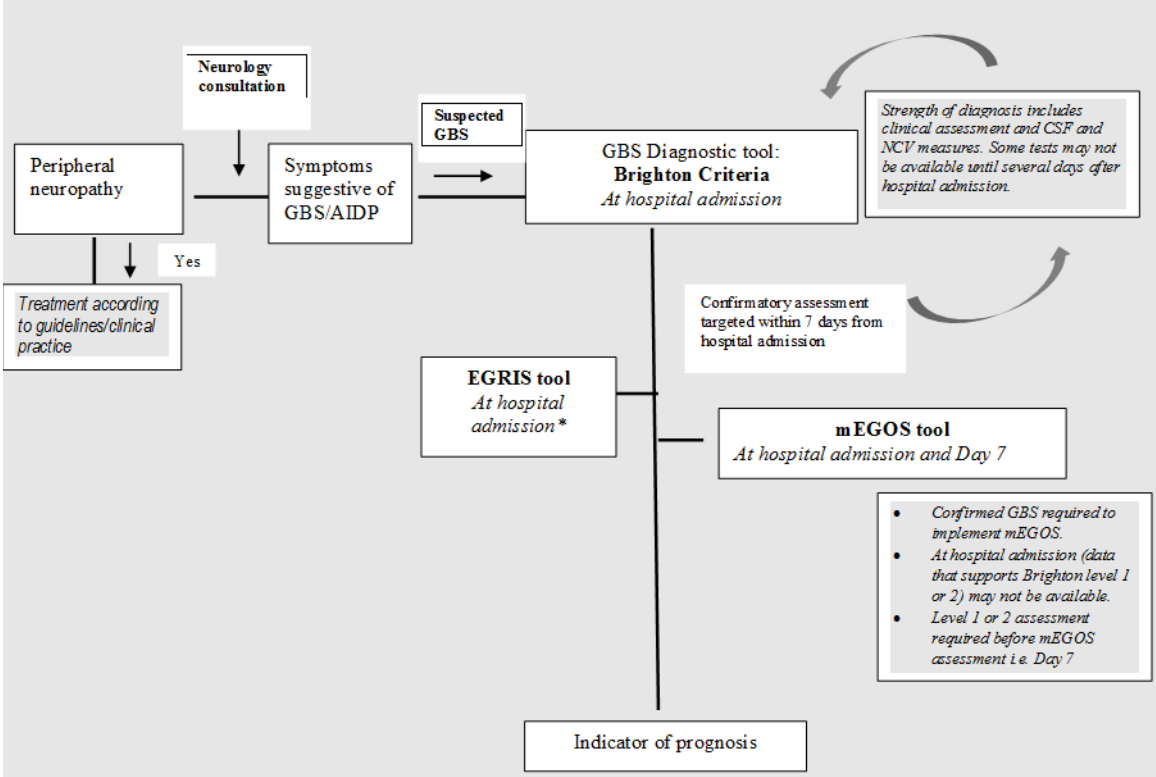
CCI

[redacted]

10.9.9. Guillain-Barré Syndrome

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

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



**Please refer to algorithm for treatment described in Figure 4.*

10.9.9.1. Neurological symptoms

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

- Progressive weakness in legs and arms (sometimes initially only in legs).
- Areflexia (or decreased tendon reflexes) in weak limbs.

Additional symptoms

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

10.9.9.2. Brighton key diagnostic criteria

At admission and confirmation within 7 days of admission

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

10.9.9.3. Erasmus GBS Respiratory Insufficiency Score (EGRIS)

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

Parameters required at hospital admission:

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

10.9.9.4. Modified Erasmus GBS Outcomes Score (mEGOS)

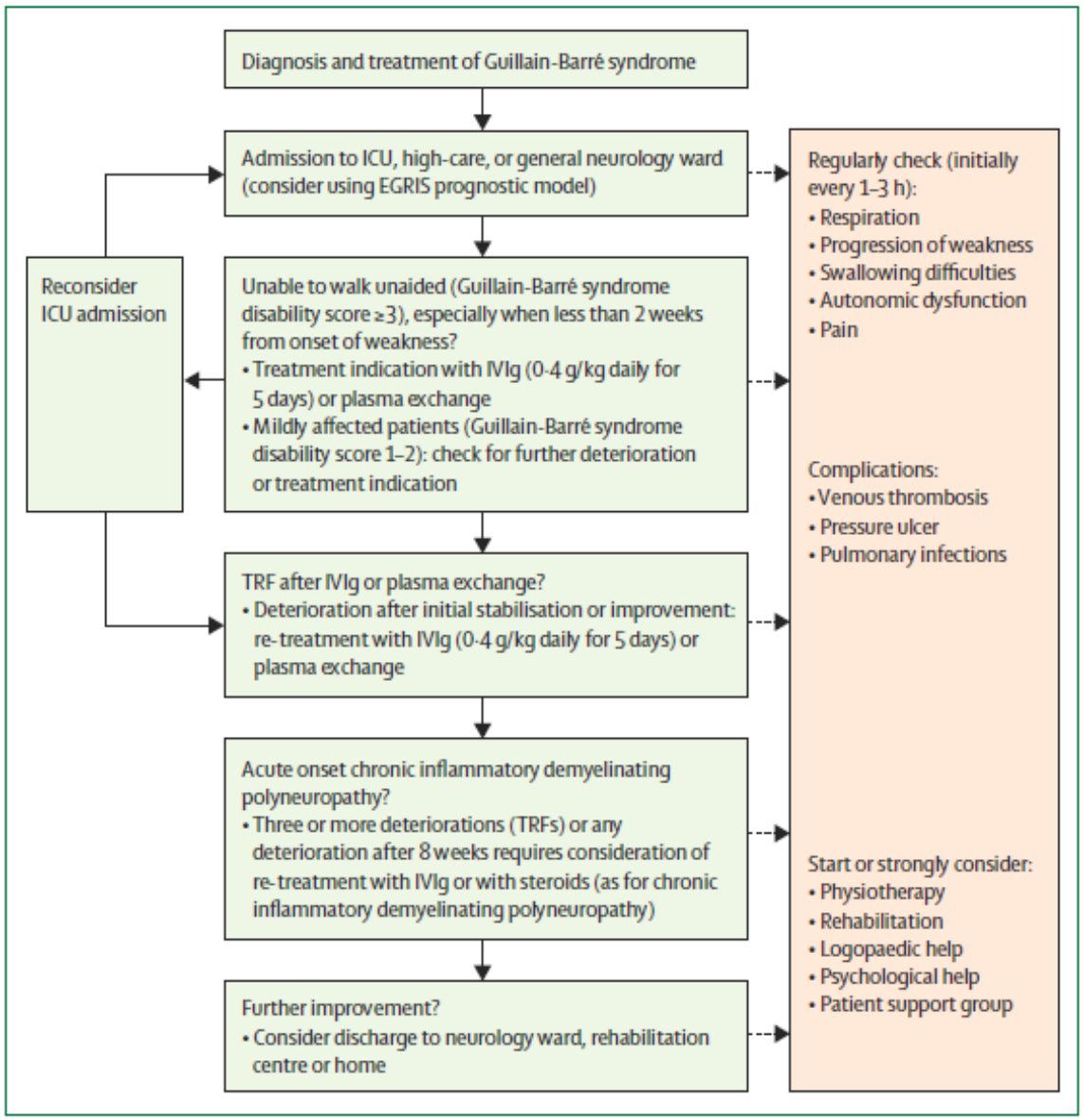
Parameters required at hospital admission and 7 days later [Walgaard, 2011]:

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

10.9.9.5. Summary of diagnosis and treatment for GBS

Additional information on the diagnosis and management of GBS (Figure 4) can be found in a review article on GBS [Willison, 2016].

Figure 4 Diagnosis and Treatment of Guillain-Barré Syndrome (GBS)



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

10.9.10. Lymphodepleting Chemotherapy Symptom Management

Cyclophosphamide and fludarabine are used as pre-conditioning lymphodepleting chemotherapy in this study. Symptoms associated with the use of cyclophosphamide and fludarabine are included in the product labels. Refer to the most current product labels, and Section 6.9.1 for details of prohibited medications.

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

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

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

10.10. Appendix 10: Guidelines for Assessment of Disease, Disease Progression, and Response Criteria

10.10.1. RECIST v1.1 Guidelines

Please note the following:

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

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

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

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

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

Guidelines for Evaluation of Disease

Measurable and Non-Measurable Definitions

Measurable Lesion:

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

≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).

≥10 mm caliper/ruler measurement by clinical exam or medical photography.

≥20 mm by chest X-ray.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured.

Non-Measurable Lesion:

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

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

Non-Measurable only Disease: The presence of only non-measurable lesions.
Note: Non-measurable only disease is not allowed per protocol.

Response Criteria

Evaluation of Target Lesions:

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

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.

- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters (e.g. percent change from Baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Applicable (NA): No target lesions at Baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

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

Evaluation of Non-target Lesions:

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

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at Baseline must be non-pathological (e.g., <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at Baseline ≥10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at Baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

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

New Lesions

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

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

Evaluation of Overall Response

Table 32 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for participants with measurable disease at Baseline.

Table 32 Evaluation of Overall Response for Participants with Measurable Disease at Baseline

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

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

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Evaluation of Best Overall Response

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

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

Confirmation Criteria:

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

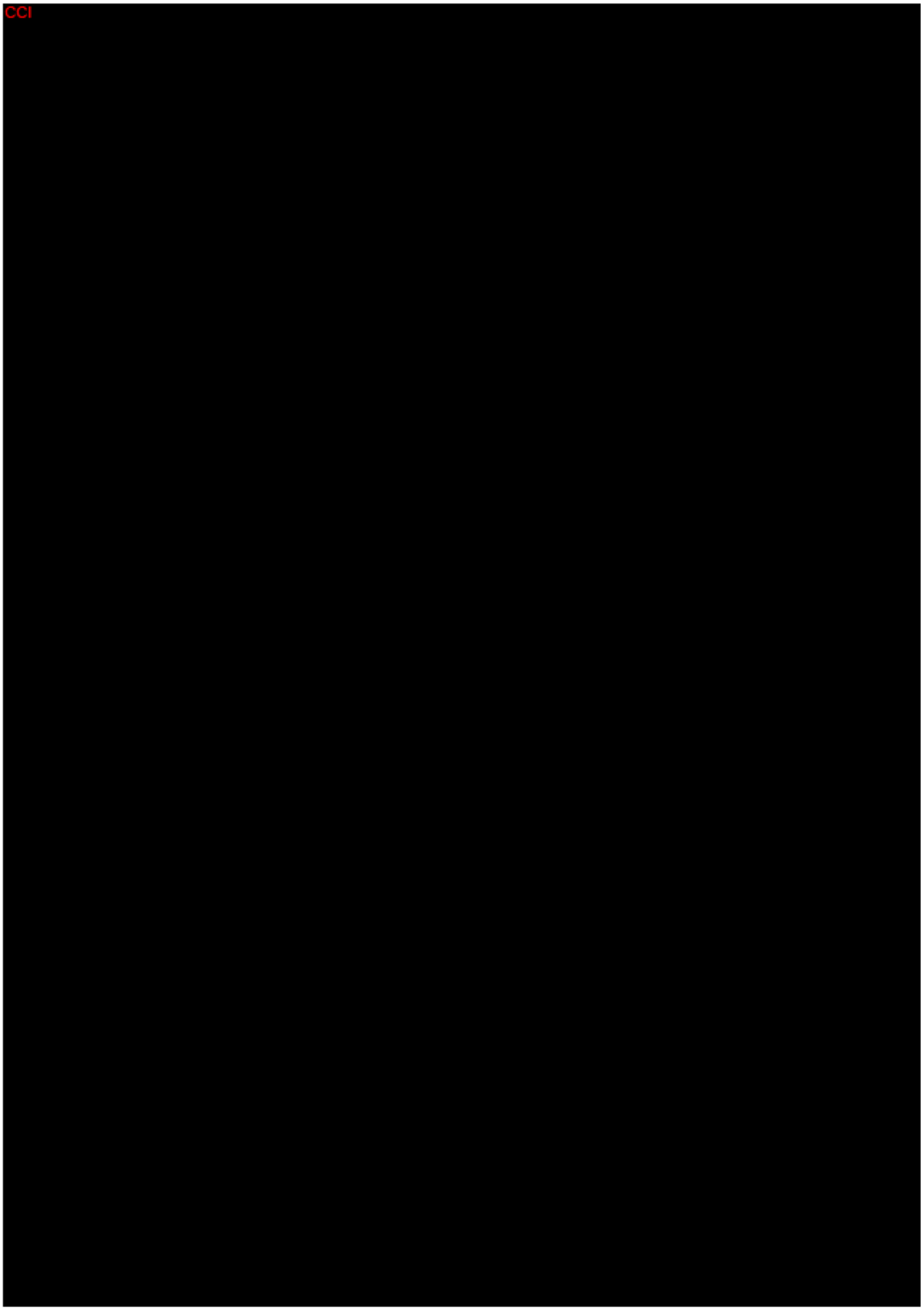

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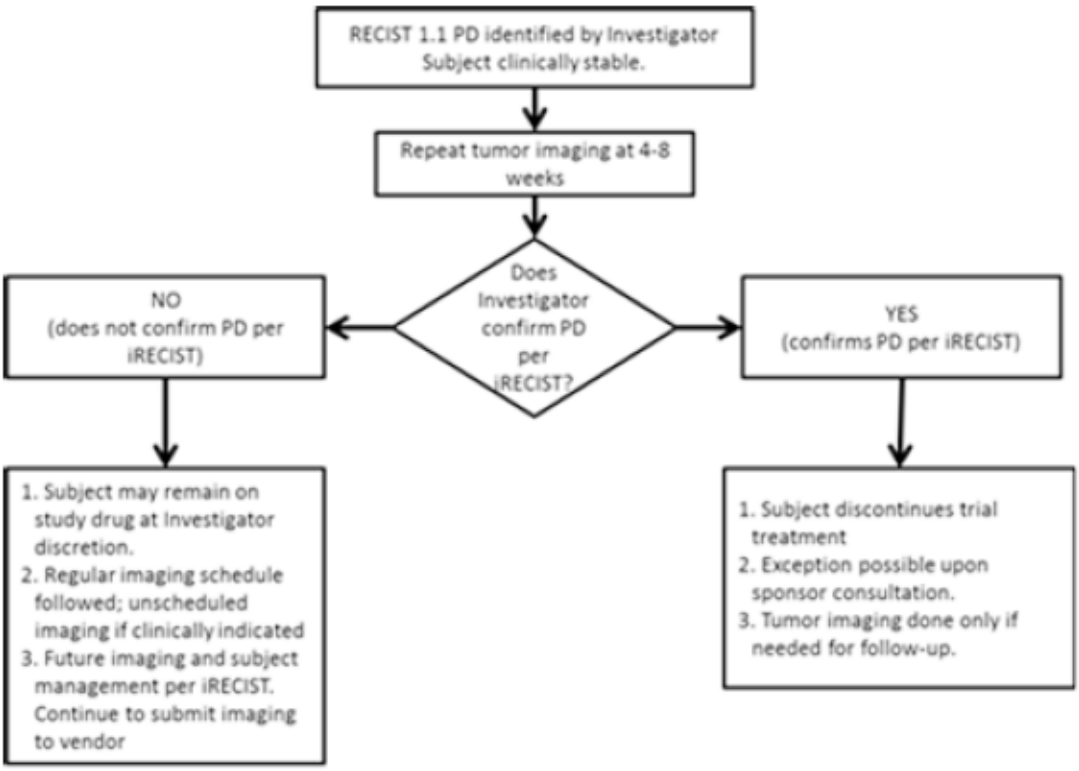
Table 33 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

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

Abbreviations: iCPD =[CCI] confirmed progressive disease; iCR =[CCI] complete response; iPR =[CCI] partial response;[CCI] = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD =[CCI] stable disease; iUPD =[CCI] unconfirmed progressive disease; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

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



Abbreviations: CCI = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; PD = progressive disease.

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 06: 17-MAY-2021

Overall Rationale for the Amendment:

The overall rationale for this amendment is to:

- Simplify/enhance screening and enrollment efforts
- Broaden patient eligibility
- Include additional safety tests and measures.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Made administrative changes and corrected clerical errors.	Changes were made for clarity and consistency
	Eliminated redundant text.	For clarity
	Replaced GSK3377794 asset number with letetresgene autoleucel / lete-cel name.	For accuracy
	Eliminated patient reported outcomes.	Decrease patient burden in non-registrational study
	Added flexibility in the collection of screening and/or baseline assessments.	Simplify protocol procedures; simplify screening and enrollment efforts and add flexibility for patient scheduling
	Added flexibility in the collection of confirmation scan following initial scan showing tumor response. Originally: from no earlier than 4 and no later than 8 weeks. Updated: no earlier than 4 to no later than the next scheduled imaging visit. Confirmation of progression will maintain 4-8 week confirmation window.	Decrease patient burden
	Updated persistence vs pharmacokinetics language	For clarity and accuracy
	Included an interim provision within the study to capture long-term follow-up data for patients who have yet to transition into the separate LTFU study. This is now considered study Part 5.	Provide a short transition period from the interventional portion of the study into the separate LTFU study for the collection of delayed AEs, persistence/RCL and survival information.
	Updated Study Design; Expanded patient eligibility to those with all actionable genetic aberrations into Arm C; Removed restriction on maximum lines of therapy for patients in all Arms; Additional safety inclusion/exclusion criteria were added for fitness of patient population.	Broaden patient eligibility

Section # and Name	Description of Change	Brief Rationale
Section 1 - Protocol Summary Section 3 - Objective and Endpoints	Updated Objectives and Endpoints language; removed language related to measures only from endpoints section; aligned language with patient population; separated secondary objectives under "efficacy" or "pharmacokinetics."	For clarity
	CCI [redacted]	
	Clarified that secondary efficacy objective will evaluate lete-cel alone and in combination with pembrolizumab.	For clarity and to align with other protocols across the lete-cel program
Section 1.3 - Schedule of Activities	Included timepoints for the collection of anti-pembrolizumab antibodies and pembrolizumab pharmacokinetics samples. Added clarifying text about the completion of EoT visit and circumstances under which CT / MRI is not required during EoT visit.	For clarity and in alignment with Merck For clarity and to decrease patient burden
Section 1.3 - Schedule of Activities Section 8.3 - Safety Monitoring	Updated persistence (for safety) and RCL testing requirements.	Align with updated FDA guidance
Section 1.3 - Schedule of Activities Section 5 - Study Population	Simplified ECG testing requirements. Added restrictions to eligibility criteria and new safety/monitoring tests.	Simplify protocol procedures Additional safety monitoring
Section 1.3 - Schedule of Activities Section 8.2.3 - Cardiac Assessments	Added serum troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) / BNP tests	Addition of cardiac biomarker tests as part of required screening/baseline visit assessments
Section 1.3 - Schedule of Activities Section 8.9.2 - Tumor Biopsies	Moved timepoint for post T-cell infusion tumor biopsy and liquid biopsy from week 7 to week 4.	Align with other protocols across the lete-cel program
Section 1.3 Schedule of Activities Section 8.11 - Patient Interviews and CCI [redacted]	Replaced the term "End-of-Study interview" with "CCI [redacted]," terms were previously used interchangeably.	For clarity and consistency within the protocol
Section 1.3 - Schedule of Activities Section 10.9.8.2 - Monitoring of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Added brain MRI as required assessment during leukapheresis eligibility screening; added flexibility in the collection of brain MRIs during baseline assessments (if more than 4 months have elapsed from last brain MRI).	Align with other protocols across the lete-cel program; align with study eligibility criteria

Section # and Name	Description of Change	Brief Rationale
Section 2.2 - Background	Updated background information.	For clarity, in alignment with other protocols across the lete-cel program and in alignment with most recent Investigator's Brochure for Lete-cel
Section 2.3 - Benefit/Risk Assessment	Updated Summary of Risks table in alignment with B/R profile for lete-cel program; Updated the Risk Assessment.	For clarity, in alignment with other protocols across the lete-cel program and in alignment with most recent Investigator's Brochure for Lete-cel
Section 4 - Study Design	Added language about aim to include approximately 5 NSCLC participants with squamous cell carcinoma (SCC) into Arms A/B.	Improve enrollment of SCC patients, if possible
Section 4.1 - Overall Design	Clarified language about assignment of participants into Arms A or B.	For clarity
Section 4.1.3 - Part 3: Lymphodepletion/Treatment Section 6.4.1 - Premedication	Clarified language about the use of antihistamines and acetaminophen prior to lete-cel infusion, following institutional guidance for dosage and specific medications.	For clarity
Section 4.1 - Overall Design Section 8.9.2 - Tumor Biopsies Section 9 - Statistical Considerations	Consolidated details about statistical considerations and tumor biopsies from Section 4.1 to Sections 9 and 8.9.2, respectively; Added further details about tumor biopsy collection requirements.	For clarity
Section 4.4 - End of Study Definition	Clarified End of Study definition; added definition for completion of interventional phase.	For clarity and to align with other protocols across the lete-cel program
Section 5 - Study Population	Re-organized layout of eligibility criteria so inclusion/exclusion efforts are assessed in the appropriate step of the participant's journey • Eligibility criteria not required to be met prior to target expression screening are now to be assessed during leukapheresis eligibility screening. • Some criteria originally required prior to lymphodepletion/treatment are now to be assessed during leukapheresis eligibility screening. • Where possible, eligibility criteria were consolidated.	Simplify protocol procedures and to align with other protocols across the lete-cel program

Section # and Name	Description of Change	Brief Rationale
Section 5.1 - Inclusion Criteria	Eliminated restrictions on when leukapheresis can be collected.	For clarity, to align with other protocols across the lete-cel program
	Updated disease progression requirements from inclusion criteria. Eliminated requirement that stated: progression has been documented within 12 weeks from the last dose of PD-1/PD-L1 checkpoint blockade therapy.	Broaden patient eligibility
	Updated predicted life expectancy requirements from ≥3 months at screening to ≥24 weeks from leukapheresis, per relevant IC.	Measures to assess patient fitness; in alignment with other protocols across the lete-cel program
	Eliminated flexibility for left ventricular ejection fraction (LVEF) requirements according to institutional standards for relevant IC; Updated requirement to ≥45%.	Consistency across sites, in alignment with other protocols across the lete-cel program
	Provided more details for the calculation of creatinine clearance, depending on age of participants. CKD-EPI formula was moved up from appendix.	For clarity, to align with other protocols across the lete-cel program
Section 5.2 - Exclusion Criteria	Updated exclusion criterion on history of prior malignancies. Criterion now lists specific malignancies.	For clarity
	Further restricted exclusion criterion for prior prior allogeneic/autologous bone marrow or solid organ transplantation.	Measures to assess patient fitness
	Updated testing requirements for active EBV infection in exclusion criteria.	For clarity and in alignment with other GSK cell therapy studies
	Updated exclusion criterion on history of allergic reactions to agents used in the study, to include dimethylsulfoxide (DMSO).	In alignment with investigator's brochure
	Updated restricitions to prior radiotherapy prior to leukapheresis and lymphodepletion/treatment.	Additional safety monitoring and in alignment with other GSK cell therapy studies

Section # and Name	Description of Change	Brief Rationale
Section 5.2 - Exclusion Criteria (Concomitant Treatments and Washout Periods)	Added Tyrosine kinase inhibitors (TKIs) to table. Corrected washout period for investigational treatment, for alignment within the protocol. Removed gene therapy and allogeneic hematopoietic stem cell transplant from table for 'Concomitant Treatments and Washout Periods."	For clarity, TKIs were missing from Concomitant Treatments and Washout Periods For clarity These treatments are not allowed, per Section 5, hence no washout period needed
Section 5.3.3 - Contraception Section 8.4.7 - Pregnancy	Included additional contraception requirements applicable to the use of fludarabine and cyclophosphamide chemotherapies. Added instruction to Investigator to advise participants on the conservation of sperm prior to initiating treatment. For participants who have persisting lete-cel beyond 12 months post infusion: once persistence test results show below level of detection for 2 consecutive times, Sponsor will notify the site that contraception period requirement is over.	Clarification of contraception requirements
Section 6.3 - Lymphodepleting Chemotherapy	Added restrictions to the recommended lymphodepleting regimen, depending on participant's medical history. Decreased fludarabine dose for patients with creatinine clearance between 30-50mL/min. Baseline assessments may be completed between Day -17 and Day -8 among participants who initiate the lymphodepleting regimen on Day -7. Added information about lymphodepletion dose calculation and creatinine clearance dose calculation. Added information for cyclophosphamide dose adjustment based on weight.	Additional safety monitoring Provide flexibility in baseline screening efforts For clarity For clarity
Section 6.4.2 - Lete-cel dose	Added clarifying language for situations in which manufacturing of lete-cel has yielded less than the minimum target dose.	For clarity

Section # and Name	Description of Change	Brief Rationale
Section 6.4.3 - Lete-cel Administration	Added language emphasizing that leukoreduction filters must not be used for the infusion of Lete-cel.	For clarity
Section 6.9.1 - Prohibited Concomitant Medication and Treatment	Addition of language prohibiting the administration of live vaccines during lymphodepletion and treatment, and for at least three months after.	In alignment with other protocols across the lete-cel program
Section 6.9.2 - Permitted Concomitant Medication and Treatment	Added request to consult Sponsor before immunizing a study participant against SAR-CoV-2 (COVID-19). Added “recommendations for participants on therapeutic anticoagulants.”	In alignment with other protocols across the lete-cel program
Section 6.10.2 - Guidelines for Pembrolizumab Withholding and Discontinuation	Updated Table 15 - Dose Modification Guidelines and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Study Treatment, at the request of Merck, supplier of pembrolizumab.	At the request of Merck
Section 7.1.3 - Temporary Discontinuation	Updated language on infusion related reactions	For clarity and to align with other protocols across the lete-cel program
Section 8.1.1 - Tumor Response Assessments	Included additional details about the handling and transfer of tumor images. Included additional language for non-contrast enhanced CT if participant is contraindicated for contrast scans or if they have renal compromise.	For clarity
Section 8.3 - Safety Monitoring	Updated definition of Delayed AEs to align with updated FDA guidance [FDA, 2020a].	Updated definitions of 6 categories of delayed AEs per FDA
Section 8.4.4 - Adverse Events of Special Interest	Included AESI of Gr 4 neutropenia lasting > 28 days	Additional safety monitoring
Section 9 - Statistical Considerations	Updated the statistical considerations for the study, in alignment with changes in the patient population and changes to standard of care. Amended analysis population definitions.	For accuracy Align with other protocols across the lete-cel program

Section # and Name	Description of Change	Brief Rationale
Section 10.2 - Appendix 2 - Clinical Laboratory Tests	Clarified that either BUN or Urea can be completed as part of clinical chemistry tests. Addition of Fibrinogen as part of the Coagulation test requirements. Addition of Ferritin, serum troponin, NT-proBNP / BNP as part of the Other Tests.	Align with other protocols across the lete-cel program
Section 10.9 - Appendix 9 Supportive Care Guidance	Added further details about hospitalization for T-cell infusion.	For clarity and to align with other protocols across the lete-cel program
Section 10.3.4 - Recording and Follow-Up on AE and SAE Section 10.9.5 - Management of Cytokine Release Syndrome Section 10.9.8 - Management of ICANS	Addition of monitoring requirements and management recommendations for suspected CRS and/or ICANS. CRS grading will be based on Lee, 2019 and include Fever, Hypoxia and Hypotension. Organ toxicities associated with CRS will be graded according to NCI-CTCAE v5.0 and do not influence CRS grading. ICANS grading will be based on Lee, 2019.	Align with SITC 2020 guidelines on immune effector cell-related adverse events
Section 10.3.5 - Reporting of SAE to GSK	Removed 72 hr requirement for the Investigator to verify relationship between each SAE and IP/study participation. Investigator must still document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.	For clarity
Section 10.10.1 - RECIST v1.1 Guidelines	Added details about RECIST v1.1 assessments.	For clarity

Amendment 05: 21-FEB-2020

Overall Rationale for the Amendment:

The overall rationale for this amendment is to add clarification regarding measurable lesion, to remove docetaxel as exclusion criterion and add platinum-based combination chemotherapy as an inclusion criterion. Docetaxel therapy as supportive therapy between leukapheresis and the start of lymphodepletion is removed.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Made administrative changes and corrected clerical errors.	Changes were made for clarity and consistency

Section 1.3-Schedule of Assessments Section 4.1-Overall Design Section 5.1.1-Inclusion Criteria Section 8.0 – Study assessments and procedures Section 8.9.2-Tumor Biopsies	Clarify that fresh biopsy may be considered upon consultation with GSK Medical Monitor (or designee) at screening for antigen expression	Changes were made for clarity and consistency
Section 5.1.3-Lymphodepletion / Treatment (Part 3)	Add platinum-based combination chemotherapy as an inclusion criterion Added clarification regarding measurable lesion per RECIST 1.1.	To improve protocol clarity
Section 5.2.1-Screening (Part 1)	Removal of docetaxel therapy as exclusion criterion and removal as supportive therapy between leukapheresis and the start of lymphodepletion.	Docetaxel could benefit patient as Standard of Care treatment (SoC)
Section 6.1- Leukapheresis	Blood volume collection moved to Apheresis Manual	To improve protocol clarity and align with Apheresis Manual
Section 6.2-Supportive Therapy and/or SoC Therapy Before Lymphodepletion	Removal of docetaxel therapy as supportive therapy between leukapheresis and the start of lymphodepletion.	Introduced as inclusion criterion
Section 8.2.2-Vital Signs	Added clarification that vital signs should be assessed as per the institutional standards and the same methods should be used throughout the course of the study.	To improve protocol clarity

Amendment 04 29-OCT-2019

Overall Rationale for the Amendment:

The overall rationale for this amendment is the addition of fresh biopsy collection in order to perform antigen expression screening, in absence of archival tumor tissue.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Made administrative changes and corrected clerical errors.	Changes were made for clarity and consistency
Synopsis Section 1.3-Schedule of Assessments Section 4.1-Overall Design Section 5.1.1-Inclusion Criteria Section 8.0 – Study assessments and procedures	Addition of option for fresh biopsy collection during screening for antigen expression	Change was made to include fresh biopsy collection in case archival tumor tissue is not available at the time of tumor antigen screening for enrollment.
Section 8.4.1- Time Period and Frequency for Collecting AE and SAE Information	Added clarification to AEs collected during the various parts of the study (Parts 1-4)	To improve protocol clarity

Amendment 03: 01-OCT-2019

Overall Rationale for the Amendment:

The overall rationale for this amendment is the removal of randomization to Arm A and Arm B, clarification of aspects related to participant enrollment and clarification regarding study stopping and pausing rules. These additions included modification of lymphodepleting regimen for older participants, modification of dose range and changes related to Health Canada requests including updates to both the Encephalopathy (now Immune Effector Cell-Associated Neurotoxicity or ICANS) and the CRS grading and management criteria

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Made administrative changes and corrected clerical errors.	Changes were made for clarity and consistency
Title, Study schema, Participant Flow and throughout the protocol	Remove randomization from study design.	Changes include removal of randomization to Arm A and Arm B.
Throughout the protocol	Explicitly stated that NSCLC patients with NTRK gene fusion and/or any other actionable genetic aberration that can be treated with targeted standard of care (NCCN recommended) therapy will not be included in this study.	Changes were made for clarity.
Synopsis Section 4.1-Overall design Section 5.1.1-Sccreening (Part 1) Section 5.1.2-Leukapheresis (Part 2) Section 5.2.2-Leukapheresis (Part 2) and throughout the protocol	Added language to allow enrollment to this study of participants that have already been deemed eligible for HLA alleles and NY-ESO-1 and/or LAGE-1a tumor antigen in other studies. Clarify the total number of participants to be enrolled Provide additional information regarding tumor biopsies	To allow enrollment of participants in this study. Changes were made for clarity.
Synopsis Section 4.3.2- Justification of GSK3377794 Dose Section Section 6.4.2-GSK3377794 Dose	Removed the target dose and modify range to 1 to 8 x10^9 transduced cells.	To align with other protocols across the GSK3377794 program and to improve protocol clarity

Section # and Name	Description of Change	Brief Rationale
Section 1.3-Schedule of Activities (SoA)	Made changes to Schedule of Activities.	Changes were made for clarity, to correct any incongruencies and to reflect all study assessments. Previously, some assessments were in the protocol's main text but not in the visit schedules.
Section 2.3.1-Risk assessment for GSK3377794 Section 2.3.2-Benefit for GSK3377794	Made changes to update safety profile for GSK3377794 based on GSK3377794 Investigator's Brochure 2019	Changes were made to align with GSK3377794 Investigator's Brochure 2019
Section 4.3.1-Justification of Lymphodepleting chemotherapy Section 6.3.1- Lymphodepletion Dose Modification	Added lymphodepleting regimen adjustments for participants ≥ 60 years old and participants with severe cytopenia	To improve participants safety
Section 4.3.2- Justification of GSK3377794 Dose Section 6.4.2-GSK3377794 Dose	Remove dose description for participants weighing <40kgr. All adult participants will receive a dose range of 1 to 8 × 10^9 (billion) transduced cells	To align with other protocols across the GSK3377794 program and to improve protocol clarity
Section 5.1.1-Screening (Part 1)	Added language to clarify the measurable disease is not an indispensable requirement for enrollment/leukapheresis	To improve protocol clarity
Section 5.1.3-Lymphodepletion/Treatment (Part 3)	Added language to clarify the measurable disease per RECIST v1.1 requirement for lymphodepletion/treatment	To improve protocol clarity
Section 5.2.1-Screening (Part 1) Section 6.2-Supportive Therapy and/or SoC Therapy Before Lymphodepletion	Added language to Docetaxel therapy as supportive therapy between leukapheresis and the start of lymphodepletion	To improve protocol clarity
Section 5.2.1-Screening (Part 1)	Added language to clarify active infections that are part of exclusion criteria	To improve protocol clarity
Section 6.3.1 Lymphodepletion Dose Modification	Added lymphodepleting regimen adjustments for participants ≥60 years old and participants with severe cytopenia	To improve participants safety
Section 7.1- Discontinuation of study intervention	Revised Study stopping and pausing rules	To align with other protocols across the GSK3377794 program
Section 8-Screening Assessments	Clarify that Liquid Biopsy (Blood Sample) is an optional assessment Total blood volume updated to 500ml	To improve protocol clarity

Section # and Name	Description of Change	Brief Rationale
Section 8.1.2-Long-Term Follow-up Section 8.4.5- Reporting Criteria during Long-Term Follow-Up (Years 1 through 15)	Include definition and reporting of delayed adverse events	To improve protocol clarity
Section 8.3.1.1-Mandated Study Pause Due to Guillain-Barré Syndrome (GBS)	Revised language to utilize diagnostic guidance for GBS [Fokke, 2014]	To align with other protocols across the GSK3377794 program
Section 8.4.1- Time Period and Frequency for Collecting AE and SAE Information	Added clarification to AEs collected during the various parts of the study (Parts 1-4)	To improve protocol clarity
Section 8.4.4- Adverse Events of Special Interest (AESIs)	Added clarification to AESIs collected during the various parts of the study (Parts 1-4)	To improve protocol clarity
Section 8.4.7-Pregnancy	Added clarification regarding contraception period for participants that received pembrolizumab	To improve protocol clarity
Section 8.9-Biomarkers	Added mutational analyses at Baseline visit as clinical biomarker assessment	To improve protocol clarity
Section 8.9.9-Stool Collection for Microbiome Analysis and Section 1.3-Schedule of Activities (SoA)	Included Stool collection for Microbiome Analysis	Evaluate stool microbiome composition and associate with response to treatment
Section 10.9.5 Management of Cytokine Release Syndrome (CRS)	Revised guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system	Changes were based on Regulatory Agency feedback
Section 10.9.8-Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Revised guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system [Lee, 2019]	Changes were based on Regulatory Agency feedback
Section 10.9.9- Guillain-Barré Syndrome (GBS)	Revised language to utilize diagnostic guidance for GBS [Fokke, 2014; Walgaard 2010; Walgaard, 2011]	To improve protocol clarity and safety monitoring

Abbreviations: AESIs: Adverse Events of Special Interest GBS: Guillain-Barré Syndrome; ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome; NRTK: Neurotrophic Tropomyosin-Related Kinase;

Amendment 02: 13-FEB-2019

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Made administrative changes and corrected clerical errors.	Changes were made for clarity and consistency.
Throughout the protocol	Participants that receive Pembrolizumab Therapy Following Disease Progression after GSK3377794 Infusion are described as Part 4 Arm A Only.	Changes were made for clarity.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Explicitly stated that NSCLC patients with BRAF, HER2, and/or any other actionable genetic aberration that can be treated with targeted standard of care (NCCN recommended) therapy will not be included in this study.	Changes were made for clarity.
Throughout the protocol	Described participants as either having NSCLC with WT EGFR and WT ALK/ROS1 or NSCLC with EGFR or ALK/ROS1 aberration.	Changes were made for clarity (to clearly contrast the two types of participants).
Throughout the protocol	Deleted references to KEYTRUDA Package Insert 2017 and deleted premedication before the first pembrolizumab infusion.	Changes were made because they were requested by Merck.
Section 1.1-Synopsis Section 1.2-Schema Section 2.2-Background Section 3.0-Objectives and Endpoints Section 4.1-Overall Design Section 5.0-Study Population Section 6.7-Measures to Minimize bias: Randomization and Blinding	Objectives/Endpoints and Schema were updated to specify WT EGFR and WT ALK/ROS1 NSCLC in Arms A and B, and EGFR or ALK/ROS1 aberration NSCLC in Arm C.	Changes were made to study design to include patients with specific molecular characteristics.
Section 1.1-Synopsis	Number of Participants changed from 44 to 45, 15 participants per arm.	Changes were made to accommodate changes in study design and addition of Arm C.
Section 1.3-Schedule of Activities (SoA)	Made changes to Schedule of Activities.	Changes were made for clarity, to correct any incongruencies and to reflect all study assessments. Previously, some assessments were in the protocol's main text but not in the visit schedules.
Section 2.2.3-Rationale for the Combination Regimen Section 4.1-Overall Design	Made changes to clarify previous lines of treatment.	Changes were made for clarity, to correct any incongruencies and accommodate changes in study design.

Section # and Name	Description of Change	Brief Rationale
Section 4.1-Overall Design	Text was added to describe in detail: • Parts 1-4 of study and Arm C • Screening process and steps • Leukapheresis/Manufacture requirements and timelines • Lymphodepletion requirements • Need for G-CSF, Mesna, antihistamines and acetaminophen administration • Storage timelines of apheresis and/or drug product	Changes were made for clarity and to describe changes in study design regarding Arm A, B and C participants.
Section 4.4.1-Treatment Completion	Text was added to describe completion of treatment phase of the study for Arms A, B and C.	Changes were made for clarity, to correct any incongruencies.
Section 4.1- Overall Design Section 5.1-Inclusion Criteria Section 5.2-Exclusion Criteria	Text was added to: • clarify the timing and process of screening assessments • inclusion and exclusion (Part 1, Part 2 and Part 3 of study conduct) criteria stating the intended participant population, specified participants should have previously received and failed appropriate target therapy per NCCN guidelines • define “intolerant” to chemo-radiotherapy • clarify the number and type of prior therapies • update Table 10 (Adequate Organ Function) • exclusion criteria for infectious diseases	Changes were made for clarity and/or because they were requested by the Regulatory Agency.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	The word “rescue” in association with pembrolizumab given to Arm A participants who have progressive disease after GSK3377794 infusion was removed. Where the abbreviation R was used for “Rescue” this is now being replaced with letter P to denote Pembrolizumab administration for Arm A participants that receive Pembrolizumab following progression after GSK3377794 infusion.	Change was requested by the Regulatory Agency.
Section 4.1 Overall Design	Text was added to explain the meaning of “prior standard of care therapy refused” by a participant.	Change was requested by the Regulatory Agency.
Section 4.1 Overall Design and Section 4.4.1 Treatment Completion	Text was included to explain “on study” for participants who receive pembrolizumab after disease progression after GSK3377794 infusion in Arm A.	Text was added for clarity.
Section 5.1.3- Lymphodepletion/Treatment (Part 3)	Edited Inclusion Criterion 15.	Text was edited for clarity.
Section 5.2.3- Lymphodepletion/Treatment (Part 3)	Deleted “replacement therapy (e.g., thyroxine, insulin, or” from exclusion criterion 25b.	The exclusion criterion is meant to exclude immunosuppressive therapy. The deleted items are not immunosuppressive.
Section 5.3- Lifestyle Considerations	Text was added to describe additional activities.	Text added for clarity
Section 6.1-Leukapheresis	Lymphocyte and CD3 count were removed.	Text removed to avoid redundancy with counts described in Section 5.1.2 (Leukapheresis).
Section 6.2- Supportive Therapy and/or SoC Therapy Before Lymphodepletion and throughout the protocol	Text was added to describe the intermediate SoC line of therapy allowed between leukapheresis and treatment. Nearly identical sections of text elsewhere in the protocol were edited to simply refer to Section 6.2.	Text was edited for clarity and to remove redundancy.

Section # and Name	Description of Change	Brief Rationale
Section 6.4.3-GSK3377794 Administration	Text referring to drug preparation and administration was removed because the information can be found in the Drug Product and Infusion Manual.	Redundant text (information on drug preparation and administration is described in the Drug Product and Infusion Manual) was removed.
Section 6.4.4-Pembrolizumab Therapy Following Disease Progression after GSK3377794 Infusion (Part 4, Arm A Only) Section 6.5- Pembrolizumab Infusion in Arms B and C and Part 4 Arm A Section 6.5.1- Schedule Modification Guidelines for Pembrolizumab Section 6.10.2- Guidelines for Pembrolizumab Withholding and Discontinuation	Text was updated to describe pembrolizumab administration and duration of treatment to Arm A Part 4 participants.	Text was added for clarity.
Section 6.6-Preparation/Handling/ Storage/Accountability	T-cell product storage temperature was changed to ≤ -130 °C.	Text was edited to correct any incongruency.
Section 6.9-Concomitant Therapy	Text was added to include replacement therapy and an intermediate SoC line of therapy between leukapheresis and treatment.	Text was added for clarity and consistency within the protocol.
Section 6.9.1-Prohibited Concomitant Medication and Treatment	Text about permitted steroid treatment was edited.	Text was added for clarity and consistency within the protocol.
Section 7.1-Discontinuation of Study Intervention	Group stopping criteria was updated.	Changes were based on Regulatory Agency feedback and to provide clarity.
Section 7.2-Participant discontinuation/Withdrawal from the study	Text was changed to include that further evaluation be performed at EoT Visit.	Text edited to provide clarity.

Section # and Name	Description of Change	Brief Rationale
Section 8.0-Study assessments and procedures	• Changed maximum blood volume per participant. Maximum amount will not exceed 440mL within 56 days, excluding leukapheresis. • Specified that HLA and tumor antigen assessments obtained 42 days prior to leukapheresis might be acceptable. • Baseline timeline was added. • Study and completion phase description was updated.	Text edited to provide accuracy and clarity.
Section 8.3.1-Safety Review Team (SRT)	SRT description was updated	Changes made to provide accuracy and clarity.
Section 8.3.3-TLTs for pembrolizumab	TLTs were updated.	Changes made to provide accuracy and clarity.
Section 8.4- Adverse Events and Serious Adverse Events	Text regarding MedDRA and the NCI-CTCAE was added.	Changes made per request from Merck.
Section 8.4.1- Time Period and Frequency for Collecting AE and SAE Information	Section was updated with full list of AESIs.	Changes made to provide accuracy and clarity.
Section 8.4.9-Progression of underlying malignancy	Section was added.	Section added to clarify reporting requirements for underlying disease events.
CCI [redacted]		
Section 8.11.6-End of Study Interview	Section was updated.	Changes were made for clarity and alignment with Section 1.3.
Section 9-Statistical Considerations	Section was updated.	Changes were made to accommodate changes in study design.

Section # and Name	Description of Change	Brief Rationale
Section 10.9.9-Guillain-Barré Syndrome	Section was added.	Section was added to provide guidance for management of GBS.

Amendment 01: 17-OCT-2018

Overall Rationale for the Amendment: Changes made to the protocol were requested by Regulatory Agency as a result of safety events which included 2 reports of Guillain-Barré syndrome in subjects who have received chemotherapy and GSK3377794 during clinical trials

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment	Updated Table 7. Summary of Risks and Risk-Mitigation Strategies Related to Study Treatments to include: • CRS events ≥ grade 3 will now be reported as a SAE and will be reported to GSK within 24 hrs. • Update to risk assessment to add additional risk of Guillain-Barré syndrome and other demyelinating neuropathies.	These are Regulatory Agency requested changes due to the 2 reports of Guillain-Barré syndrome
Section 5.2.1 Screening (Exclusion Criteria 'h')	Participants with prior or active demyelinating disease will now be excluded from study participation.	This is a Regulatory Agency requested change due to the 2 reports of Guillain-Barré syndrome
Added Section 8.3.1.1 Mandated Study Pause due to GBS	A mandatory pause in enrollment and stopping GSK3377794 treatment for all participants within the GSK3377794 studies has been introduced if an occurrence of GBS occurs.	This is a Regulatory Agency requested change due to the 2 reports of Guillain-Barré syndrome.
Added Section 8.3.6 Monitoring and management for Demyelinating Neuropathy and other Neurological events	Provides guidance on when a neurological consultation / evaluation is to occur for those participants receiving GSK3377794 with a Grade 2 or higher neurologic events of a ≥ 7-day duration. Further, this section provides guidance for those participants who develop signs and symptoms consistent with GBS.	These are Regulatory Agency requested changes due to the 2 reports of Guillain-Barré syndrome

Section # and Name	Description of Change	Brief Rationale
Section 8.4.4 Adverse of Special Interest (AESIs)	Added Guillain-Barré syndrome or acute demyelinating neuropathy as an AESI. Further, added reporting criteria for Grade 3 or higher CRS, and for Guillain-Barré syndrome or other demyelinating neuropathies.	These are Regulatory Agency requested changes due to the 2 reports of Guillain-Barré syndrome

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