TITLE PAGE

Protocol Title: Open-Label Pilot Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered NY-ESO-1 Specific (c259) T Cells Alone or in Combination with Pembrolizumab in HLA-A2+ Subjects with NY-ESO-1 and/or LAGE-1a Positive Relapsed and Refractory Multiple Myeloma

Protocol Number: 208470/05

Short Title: NY-ESO-1^{c259} T alone and in combination with pembrolizumab for multiple myeloma

Compound Number: GSK3377794 (also known as NY-ESO-1^{c259}T)

Sponsor Name and Legal Registered Address:

GlaxoSmithKline
5 Crescent Drive
Philadelphia, PA 19112
US

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

Regulatory Agency Identifying Number(s):

Investigational New Drug Number: 014603

Approval Date: 24-FEB-2020.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol Title: Open-Label Pilot Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered NY-ESO-1 Specific (c259) T Cells Alone or in Combination with Pembrolizumab in HLA-A2+ Subjects with NY-ESO-1 and/or LAGE-1a Positive Relapsed and Refractory Multiple Myeloma

I, the undersigned, have reviewed the protocol, including the appendices, and I will conduct the clinical study as described and will adhere to the International Conference on Harmonization (ICH) tripartite guideline E6 (R1): Guideline for Good Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the NY-ESO-1^{c259}T Investigator's Brochure.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

CLINICAL STUDY PROTOCOL

Title: Open-Label Pilot Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered NY-ESO-1 Specific (c259) T Cells Alone or in Combination with Pembrolizumab in HLA-A2+ Subjects with NY-ESO-1 and/or LAGE-1a Positive Relapsed and Refractory Multiple Myeloma

Product Name: NY-ESO-1^{c259}T

Protocol Number: GSK208470 (ADP-0011-008)

Regulatory Agency identifying Number: IND 014603

DATE OF ORIGINAL PROTOCOL 19-DEC-2016

Amendment Number	Date	Reason for Change
Amendment 1	13-Mar-2017	Integration of the Screening tests of ADP-0000-001 for HLA-genotyping and NY-ESO-1/LAGE-1a antigen expression levels in the Interventional protocol
Amendment 2	24-Jul-2018	Subsequent to the licensing of Adaptimmune product NY-ESO by GSK, the purpose of this protocol amendment is to: - Delete or replace references to Adaptimmune or its staff with that of GlaxoSmithKline (GSK) and its authorized agents to align with the change of sponsorship; - Make administrative changes to align with GSK processes and procedures; - Changes to lymphodepletion regimen throughout.
Amendment 3	17-Oct-2018	Changes made to the protocol were requested by the FDA as a result of safety events which included 2 reports of Guillain-Barré syndrome in subjects who have received chemotherapy and NY-ESO-1^{c259}T during clinical trials.
Amendment 4	19-Sep-2019	Changes related to FDA requests were made, including changes to Inclusion Criteria #5, the addition of study stopping rules, and the Encephalopathy (now Immune Effector Cell-Associated Neurotoxicity or ICANS) and the CRS grading and management criteria were updated. Also, changes were made to the lymphodepletion regimen for older subjects, and the randomization scheme was removed to enroll Arm1 (NY-ESO-1^{c259}T single infusion) subjects first.

Amendment Number	Date	Reason for Change
Amendment 5		Protocol was amended to allow subjects who undergo leukapheresis as part of Study 208470 to subsequently receive a full line of therapy with an agent targeting BCMA– potentially in a study run by another sponsor. The subject would then receive NY-ESO-1^{c259}T, after progressive disease from this intermediate BCMA-targeted therapy. The protocol was also amended to update several eligibility criteria, clarify the intent of Section 3.3.1 – study activities following lymphodepletion of third Arm 2 subject, update risk language for NY-ESO-1^{c259}and pembrolizumab, update plans for statistical analyses, and update version of International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma used in efficacy determination from 2011 version to 2016 version.

CONFIDENTIALITY STATEMENT

This document contains information which is the property of GlaxoSmithKline (GSK), and therefore is provided in confidence for your review. It is understood that this information will not be disclosed to others without written approval from GSK.

DECLARATION

This study will be conducted in compliance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

RESPONSIBLE SPONSOR STUDY PHYSICIAN/SPONSOR INFORMATION PAGE

PPD

Sponsor Signatory

PPD

(BENEDETTO FARSACI, MD) 02-24-2020

Date

FOR Hesham Abdullah, MD, MSc, RAC
Senior Vice President
Head Clinical Development – Oncology
Oncology Research and Development
GlaxoSmithKline

Sponsor Details

GlaxoSmithKline
5 Crescent Drive
Philadelphia, PA 19112
US

SYNOPSIS

Title Open-Label Pilot Study to Assess the Safety, Tolerability and Antitumor Activity of Genetically Engineered NY-ESO-1 Specific (c259) T Cells Alone or in Combination with Pembrolizumab in HLA-A2+ Subjects with NY-ESO-1 and/or LAGE-1a Positive Relapsed and Refractory Multiple Myeloma	
Short Title	NY-ESO-1^{c259} T alone and in combination with pembrolizumab for multiple myeloma
Protocol Number	GSK208470 (ADP-0011-008)
Phase	This is a pilot study.
Methodology	Subjects will undergo screening for HLA-type and for the presence of NY-ESO-1 and/or LAGE-1a antigen in their bone marrow. Only subjects who are selected after HLA-genotyping and determination of antigen expression will be considered for the eligibility screening. Subjects meeting all eligibility criteria will be assigned to a treatment Arm: NY-ESO-1^{c259}T alone (Arm 1) or NY-ESO-1^{c259}T in combination with pembrolizumab (Arm 2). Enrollment of Arm 1 will be completed before continuing enrolling subjects to Arm 2. Subjects will then undergo leukapheresis to obtain cells for the manufacture of autologous NY-ESO-1^{c259} SPEAR T cells™ (Specific Peptide Enhanced Affinity Receptor T cells). Anticancer therapy may be administered between screening and leukapheresis, and between leukapheresis and the start of lymphodepletion (bridging or intermediate therapy), if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods (see exclusion criterion 3) must be respected. When the NY-ESO-1^{c259}T product is available, subjects who have been confirmed eligible during baseline assessments period (Day -14 until Day -8) will undergo lymphodepleting chemotherapy with fludarabine on Day -8, Day -7, Day -6, and Day -5, and cyclophosphamide on Day -7, Day -6, and Day -5, followed by granulocyte-colony stimulating factor (G-CSF) support starting on Day -4 then receive the single infusion of NY-ESO-1^{c259}T (transduced cell range: 1×10^9 to 8×10^9) that will be administered on Day 1. Eligible subjects who do not receive the NY-ESO-1^{c259}T infusion for any reason may be replaced. In Arm 1, the single infusion of NY-ESO-1^{c259}T on Day 1 will be the only Investigational Product (IP) administered. In Arm 2, 3 weeks after the infusion of NY-ESO-1^{c259}T on Day 1, an initial dose of the other IP pembrolizumab will be administered on Day 22 (Week 3). The second dose of pembrolizumab will be administered three (3) weeks later at Week 6, and subsequent doses of pembrolizumab will be administered every 3 weeks thereafter up to Week 108 post T-cell infusion. If toxicities that preclude pembrolizumab treatment (such as CRS Grade ≥2) are observed at Day 22 (Week 3), infusion of pembrolizumab will start on Week 6. If toxicities have not resolved by Week 6, pembrolizumab will not be administered and the subject will be followed for visits as a subject in Arm 1.

	Safety will be assessed at each clinic visit. This is the first study investigating the safety and efficacy of the combination of NY-ESO-1^{c259}T and pembrolizumab. Treatment Limiting Toxicities (TLTs) will be evaluated for subjects in the combination arm (Arm 2). A Safety Review Team (SRT)will review safety data in both Arm 1 and Arm 2 at any time. Enrollment in Arm 2 will be paused after the third subject in Arm 2 has initiated lymphodepletion. A complete safety review of the first 3 subjects dosed with T-cells and pembrolizumab on Arm 2 will be conducted before enrollment may resume. The study may be paused to evaluate safety at any time or if at an interim assessment the predictive probability that the TLT rate at the end of the trial exceeds 33%, is greater than 50%. The SRT may recommend closing an arm of the trial at any time. Efficacy will be assessed using International Myeloma Working Group (IMWG) Uniform Response Criteria (2016) Subjects will complete the study once they have met one of the criteria to be transferred into the Long-Term Follow-Up (LTFU) protocol:subjects never dosed with pembrolizumab will be transferred once their disease progression is confirmed or 108 weeks after NY-ESO-1^{c259}- cell infusion, whichever is sooner; subjects who received pembrolizumab will in addition require to be followed for a minimum of 24 months past their last dose of pembrolizumab and monitored for 18 months for complications of post allogeneic stem cell transplant (allo-SCT) when applicable if transplant were to occur during the 24 month follow-up.
Study Duration	It is anticipated that study enrollment would be completed in approximately 18 months. The primary data analysis will be conducted after all treated subjects have been followed up for at least 6 months after NY-ESO-1^{c259}T infusion or have progressed or died or were withdrawn from the study. A subject will complete the treatment phase upon disease progression (subject to 9 weeks minimum follow-up for safety), or 108 weeks after NY-ESO-1^{c259}T-cell infusion, whichever is sooner. All subjects, completing the treatment phase, will enter a LTFU protocol. Study completion occurs when all subjects in the treatment phase of the study have been rolled over to the Long-Term Follow-Up (LTFU) protocol GSK208750 (ADP-0000-002) or died or were withdrawn from the study. The final analysis will be conducted after all subjects have completed the study or died or withdrawn. If it is believed the primary analysis will occur within 6 months of the final analysis, the primary analysis may not be performed such that there will only be the final analysis. Monitoring for adverse events (AEs) of gene therapy and overall survival will last 15 years from the time of the T-cell infusion. In addition, subjects who received pembrolizumab and undergo an allogeneic stem cell transplant within 24 months from their last pembrolizumab dose, will be followed for complications of post allo-SCT (defined in Section 9.5) for 18 months.
Study Centers	This is a multicenter study, including approximately 10 sites. Additional sites may be added at the discretion of the Sponsor.

Objectives:	**Endpoints:**
Primary	
To describe the safety and tolerability of autologous genetically modified T cells (NY-ESO-1^{c259}T) alone (**Arm 1**) or in combination with pembrolizumab (**Arm 2**) in subjects who are human leukocyte antigen HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 and/or LAGE-1a positive relapsed refractory multiple myeloma.	Adverse events (TLT rate and AEs), including serious adverse events (SAEs); laboratory assessments including chemistry, hematology and coagulation; and cardiac assessments by electrocardiogram (ECG).
Secondary	
To describe the antitumor activity of autologous genetically modified T cells (NY-ESO-1^{c259}T) alone (**Arm 1**) or in combination with pembrolizumab (**Arm 2**) in subjects who are HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 and/or LAGE-1a positive relapsed refractory multiple myeloma To describe the persistence of autologous genetically modified T cells (NY-ESO-1^{c259}T) over time	• Overall Response Rate (ORR) • Time to Response (TTR) • Duration of Response (DOR) for all subjects who achieve at least PR • Progression-free survival (PFS) • Maximum persistence (Cmax), time to Cmax (Tmax), and area under the time curve from zero to time t AUC(0-t), as data permit
Exploratory	
To describe the antitumor activity of autologous genetically modified T cells (NY-ESO-1^{c259}T) alone (**Arm 1**) or in combination with pembrolizumab (**Arm 2**) in subjects who are HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 and/or LAGE-1a positive relapsed refractory multiple myeloma.	Overall survival (OS).
To evaluate minimal residual disease (MRD) at 4 months post T-cell infusion (Week 15).	MRD rate at Week 15.
To evaluate the persistence, phenotype, and functionality of NY-ESO-1^{c259} positive T cells.	Correlate persistence, phenotype, and functionality of NY-ESO-1^{c259}T in the peripheral blood and/or bone marrow with response to treatment and safety.

To understand mechanisms of resistance to NY-ESO-1^{c259}T.	Determine whether loss of NY-ESO-1 and/or LAGE-1a expression in myeloma cells is a resistance mechanism. Correlate apparition of anti-NY-ESO-1^{c259}TCR antibodies with efficacy and safety. Correlate expression of PD-L1 in the tumor microenvironment and PD-1 expression on T cells with response to treatment. Correlate frequency of immune cell subsets in peripheral blood and/or bone marrow with treatment response. Correlate frequency of immune cell subsets in peripheral blood and in bone marrow.
To evaluate antigen spreading as a mechanism of response.	Correlate clonal outgrowth of T-cell populations with tumor response following T-cell infusion.
To evaluate cytokine levels pre- and post-infusion on cytokine release syndrome (CRS).	Correlate cytokine levels with incidence and severity of CRS or other safety events.
To evaluate the impact of germline polymorphisms in IL-6, TNF-α, IL-10, IFN-γ and TGF-β on CRS	Polymorphisms in germline deoxyribonucleic acid (DNA) will be correlated with CRS.
Number of subjects	The target enrollment for this study is approximately 24 subjects treated with NY-ESO-1^{c259}T: 12 in Arm 1 and 12 in Arm 2. Eligible subjects who do not receive the NY-ESO-1^{c259}T infusion for any reason may be replaced.
Inclusion /Exclusion Criteria	**Subject Inclusion Criteria** A subject must meet the following inclusion criteria to be eligible for participation in this study: **Screening (Part 1):** 1. Subject has voluntarily agreed to participate by giving written informed consent for the screening process in accordance with ICH GCP Guidelines and applicable local regulations. 2. Subject has voluntarily agreed to abide by all protocol required procedures including study related assessments, and

	management by the treating institution for the duration of the study and long-term follow-up. 3. Subjects must be 18 years of age or older at the date of consent. 4. Histologically confirmed diagnosis of secretory multiple myeloma (must have measurable M protein in serum or urine) with at least one of the following: • Serum M- protein ≥0.5 g/dL (≥5 g/L) for IgG, IgM, IgA, or ≥0.05 g/dL for IgD; or • Urine M-protein ≥200 mg/24 hours ; or • Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65). 5. Subject must have documented diagnosis of relapsed and refractory multiple myeloma (RRMM) as described below: • subjects who have received at least 3 prior regimens and, • were responsive to at least 1 or more prior regimens (as defined by IMWG criteria), and • are refractory to their most recent therapy (≤ 25% response or progression during therapy or within 60 days after completion of therapy). Prior therapies for subjects with RRMM must have contained at least one drug from each of the following drug classes: an immunomodulatory imide drug (IMiD), proteasome inhibitor, alkylator (unless the subject is ineligible or contraindicated to receive an alkylator), CD38 monoclonal antibody, and glucocorticoid as separate lines or a combined line of therapy. If prior therapy includes autologous stem cell transplantation (ASCT), then induction/ASCT/maintenance therapies will be considered as one line of therapy altogether. Subjects who have relapsed after ASCT or are unable to receive ASCT are eligible. The interval from ASCT to entry in the study must be ≥12 weeks. 6. Left ventricular ejection fraction (LVEF) ≥50%. A lower LVEF (≥40%) is permissible if a formal cardiologic evaluation reveals no evidence for clinically significant functional impairment, otherwise the subject may not enter the study. 7. For subjects who have received prior checkpoint inhibitors or other immuno-oncology agents like T-cell receptor agonists:

	• Subjects with endocrine AE of any grade are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic. • Must not have experienced any ≥ Grade 3 AE nor any neurologic AE of any grade while receiving prior checkpoint inhibitors. • Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE related to checkpoint inhibitors, not have experienced recurrence of an AE related to checkpoint inhibitors if re-challenged, and not currently require maintenance doses of corticosteroids. 8. Subject has Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. **Leukapheresis/Manufacturing (Part 2):** All screening criteria must be reviewed and fulfilled along with all of the following criteria prior to leukapheresis. Leukapheresis may not be necessary for subject for whom NY-ESO-1^{c259}T-cell product is already manufactured. 9. Subject is HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive as determined by a central laboratory. (This determination will be made under a pre-enrollment screening informed consent form [ICF]. There are no restrictions on the timing of HLA typing for screening and data can be taken from subjects' records.. 10. Subject has confirmed sufficient expression of NY-ESO-1 and/or LAGE-1a by reverse transcription polymerase chain reaction (RT-PCR) as determined by a central laboratory contracted by the Sponsor (this determination will be made under a pre-enrollment screening ICF). 11. Subject has voluntarily agreed to participate by giving written informed consent for treatment in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and applicable local regulations. 12. In the Investigator's opinion, the subject is fit for cell collection. 13. The subject has the following laboratory parameters determined prior to leukapheresis according to timelines in the Apheresis Manual and which meet the requirements in the table below:

Absolute neutrophil count (ANC)	≥1.0 x 10^9/L
CD3 count	≥200/µL
Lymphocyte count	≥0.5 x 10^9/L

Lymphodepletion / Treatment (Part 3)

All prior inclusion criteria described for Screening and Leukapheresis must be reviewed and fulfilled along with the following criteria prior to lymphodepletion.

14. Subject has adequate vital organ function as indicated by the following laboratory values in the table below. Specimens must be collected no more than 7 days prior to start of lymphodepletion.

System	**Laboratory Value**
Hematological	
Absolute Neutrophil count (ANC)	≥1.0 × 10^9/L (without G-CSF support)
Platelets[a]	≥50 × 10^9/L
Hemoglobin	>80 g/L (8 g/dL) (without transfusion support within 7 days from start of leukapheresis)
Coagulation	
Prothrombin time (PT)[b] or International Normalized Ratio (INR)	≤1.5 × upper limit of normal (ULN)
Partial thromboplastin time (PTT)[b]	≤1.5 × ULN
Renal	
Measured or calculated[c] creatinine clearance	≥30 mL/min and not on dialysis
Hepatic	
Serum total bilirubin	≤1.5 × ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)
Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT)	≤2.5× ULN

Alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT)	

a. Subjects should not have received platelet transfusion within 2 weeks of screening blood count.
b. Unless receiving therapeutic anticoagulation, in which case PT or PTT should be within therapeutic range of intended use of anticoagulants.
c. Subjects who are >18 or <65 years of age can be assessed using estimated creatinine clearance calculated using the Chronic kidney disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009]:

GFR = 141 x min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black] where, Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min (Scr /κ, 1) indicates the minimum of Scr /κ or 1, and max (Scr /κ, 1) indicates the maximum of Scr /κ or 1.

Subjects ≥65 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.

15. Subject previously treated with BCMA therapy (BCMA CAR-T, ADC, or other type of BCMA-targeted therapy) must have progressed from this therapy prior to attending the Baseline visit prior to beginning lymphodepletion.

16. Contraception used by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    - Male subjects:

    Male subjects are eligible to participate if they agree to the following during the period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer.

    - Refrain from donating sperm

    Plus either:

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

    OR

    - Must agree to use contraception/barrier as detailed below
    - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak when having sexual intercourse with a woman of

	childbearing potential (WOCBP) who is not currently pregnant. o Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person. • Female subjects: A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: o Is not a WOCBP as defined in Section 6.3.3 OR o Is a WOCBP (as defined in Section 6.3.3) and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Section 6.3.3 during the period starting at the Baseline Visit, for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer. If assigned to Arm 2 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 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. o 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 subject must be excluded from participation if the serum pregnancy result is positive. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

	Subject Exclusion Criteria A subject meeting any of the following criteria is not eligible for participation in the study. **Screening (Part 1):** 1. Subjects with only plasmacytomas, plasma cell leukemia, monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), non-secretory myeloma or primarily amyloidosis. 2. Subject has already received one of the following therapy/treatment: anti-PD-1, anti-PD-L1, or anti-PD-L2 inhibitor. Note: this exclusion only applies to subjects that would be assigned to Arm 2. 3. Subjects who have previously participated in Merck pivotal trial NCT02576977: Study of Pomalidomide and Low Dose Dexamethasone With or Without Pembrolizumab (MK-3475) in Refractory or Relapsed and Refractory Multiple Myeloma (RRMM) (MK-3475-183/KEYNOTE-183). 4. Subject has received a prior allogeneic stem cell transplant. 5. Subject has toxicity from previous anticancer therapy that has not recovered to ≤ Grade 1 or to their baseline level of organ function (as outlined in Subject Inclusion Criteria 14) prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g. peripheral neuropathy) can be enrolled on a case-by-case basis with prior consultation and agreement with the Sponsor Study Physician. 6. Subject had major surgery within 4 weeks prior to enrollment (kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities. 7. Subject has history of allergic reactions attributed to fludarabine, cyclophosphamide, or agents similar in chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study. 8. Known history of myelodysplasia. 9. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).

	NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice or cirrhosis. 10. Known history of chronic active hepatitis or liver cirrhosis (if suspected by laboratory studies, should be confirmed by liver biopsy). 11. Subject has an active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human T-lymphotropic virus (HTLV) as defined below: • Positive serology for HIV. • Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of chemotheraphy. • Active hepatitis C subjects as demonstrated by test for hepatitis C ribonucleic acid (RNA). Subjects who are HCV antibody positive will be screened for HCV RNA by any RT-PCR or by DNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value. • Positive serology for HTLV 1 or 2. Re-screening for infection disease markers is not required at baseline (prior to lymphodepleting chemotherapy) 12. History of severe immune disease, including non-infectious pneumonitis, requiring steroids or other immunosuppressive treatments. 13. Active immune-mediated diseases including: a. Connective tissue diseases, uveitis, sarcoidosis, inflammatory bowel disease, multiple sclerosis, (non-infectious) pneumonitis. b. Prior or active demyelinating disease. 14. Evidence or history of significant cardiac disease (such as, but not limited to, unstable angina pectoris, myocardial infarction within the prior 6 months, heart failure within 6 months, symptomatic congestive heart failure, symptomatic or uncontrolled arrhythmias, severe aortic stenosis, symptomatic mitral stenosis). 15. QTc > 450 msec or QTc > 480 msec for patients with bundle branch block. NOTES:

	• The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. • The specific formula that will be used to determine eligibility and discontinuation for an individual subject 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 subject and then the lowest QTc value used to include or discontinue the subject from the trial. • For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP). 16. Evidence or history of other significant, hepatic, renal, ophthalmologic, psychiatric, or gastrointestinal disease which would likely increase the risks of participating in the study. 17. Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers, carcinoma in situ of the breast, treated superficial bladder cancer or prostate cancer, or in situ cervical cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period. Long-term adjuvant therapy (example: breast cancer) is acceptable. 18. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. 19. Active bacterial or systemic viral or fungal infections 20. Pregnant or breastfeeding. **Leukapheresis/Manufacturing (Part 2)** 21. The subject has received or plans to receive the following treatment regimens and does not or cannot meet the specified time frames prior to leukapheresis or lymphodepleting chemotherapy:

Treatment/Therapy	Required Wash-out
Cytotoxic chemotherapy	2 weeks
Immune therapy (including monoclonal antibody therapy)	No wash-out
Immunomodulator imide therapy (IMiD e.g. lenalidomide or pomalidomide)	No wash-out
Proteasome inhibitor therapy (e.g. bortezomib or carfilzomib)	2 weeks
Anticancer Vaccine	4 weeks The subject should be excluded if the Investigator considers their disease is responding to an experimental vaccine given within 6 months
Live-virus vaccination. NOTE: Seasonal flu vaccines that do not contain live virus are not an exclusion.	4 weeks
Allogeneic hematopoietic stem cell transplant at any time	Not permitted
Corticosteroids or any other immunosuppressive therapy. NOTE: Use of inhaled or topical steroids, or of physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency is permitted.	2 weeks
Genetically engineered cell therapy	12 weeks
Investigational treatment	4 weeks or 5 half-lives, whichever is longer
Radiotherapy	2 weeks
NOTE: Duration of any other anticancer therapies must be discussed with the Sponsor Study Physician	

Lymphodepletion/Treatment (Part 3):

A subject is not eligible for lymphodepletion if any of exclusion criteria for screening or leukapheresis or any of the following parameters apply:

22. More than two years have passed since the last leukapheresis collection.

Study Product, Dose, Route, Regimen	The two IPs in this study are: • NY-ESO-1^{c259}T, an autologous T cell transduced with a self-inactivating lentivirus encoding for a high affinity NY-ESO-1/LAGE-1a-specific T-cell receptor (TCR). The "c259" designation refers to the optimized affinity clone. • Pembrolizumab [Keytruda USPI, 2020], a humanized monoclonal antibody against the PD-1 protein. Fludarabine 30 mg/m^2/day on Days -8, -7, -6, and -5 over 30 minutes, and cyclophosphamide 900 mg/m^2/day on Days -7, -6, and -5 intravenously (over 1 hour) will be used for lymphodepletion prior to the study treatment (see dose modification for patients over 60 years of age). G-CSF will be given to all subjects 24 hours after the last dose of cyclophosphamide. **Arm 1:** Subjects will receive NY-ESO-1^{c259}T alone. A single infusion of NY-ESO-1^{c259}T will be administered on Day 1, which is 4 days after completing the cyclophosphamide and fludarabine (there is no Day 0 for this study). **Arm 2:** Subjects will receive NY-ESO-1^{c259}T in combination with pembrolizumab. A single infusion of NY-ESO-1^{c259}T will be administered on Day 1, which is 4 days after completing the cyclophosphamide and fludarabine (there is no Day 0 for this study). The first dose of pembrolizumab will be administered on Day 22, 3 weeks later. The second dose of pembrolizumab will be administered at Week 6 and subsequent doses of pembrolizumab will be administered every 3 weeks thereafter, up to Week 108 post-infusion. If toxicities that preclude pembrolizumab treatment (such as CRS Grade ≥2) are observed at Day 22 (Week 3), infusion of pembrolizumab will start on Week 6. If toxicities have not resolved by Week 6, pembrolizumab will not be administered and the subject will be followed for visits as a subject in Arm 1. Pembrolizumab (200 mg) is administered as an intravenous infusion over 30 min. NY-ESO-1^{c259}T is administered as a transduced cell dose in the range of 1 x 10^9 to 8 x 10^9 transduced cells. If the transduced cell dose is less than the minimum dose, manufacturing of additional transduced T cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range. In the event that no banked leukapheresis product is available a second leukapheresis may be performed.
Comparator therapy	None
Statistical Methodology	Eligible subjects will be assigned to either Arm 1 or Arm 2. Subjects who do not receive the NY-ESO-1^{c259}T infusion for any reason may be replaced. Safety will be summarized using descriptive statistics and listings and reviewed throughout the trial. As subjects are accrued and at n≥3 treated with both NY-ESO-1^{c259}T and pembrolizumab, Bayesian predictive probabilities will be used to evaluate TLTs for the combination. If (at n < N_{max}=10) the probability that the TLT rate exceeds 0.33 at the end of the trial is greater than

	0.50, the SRT may recommend to pause the study to review safety and if warranted, to stop an arm or the trial for safety. Summary statistics will be provided for each arm. The study is not powered to compare safety or efficacy between the arms and therefore no formal statistical comparisons between arms is planned. 95% two-sided confidence intervals may be calculated for selected endpoints for estimation purposes. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and proportions. Graphical summaries of the data may be presented. Interim analyses to inform internal decision making may be performed for each arm after enrollment to the arm is complete and all the enrolled subjects in that arm who will receive NY-ESO-1^{c259}T have done so and of those: all have completed at least three disease assessments since infusion or have progressed (and if progressed prior to the Week 9 visit, have been followed up for safety for a minimum of 9 weeks following T-cell infusion) or have died or were withdrawn from the study. A further analysis once all Arm 1 subjects satisfy the criteria for the primary analysis may also be undertaken.

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1. BACKGROUND AND STUDY RATIONALE

1.1. Adoptive T-cell Therapy

Adoptive T-cell therapy (ACT) is a treatment that uses a cancer subject's own T lymphocytes with antitumor activity, expanded *in vitro* and re-infused into the subject. The ultimate objective of the process is the stimulation and expansion of potent and antigen-specific T-cell immunity. There are numerous recent publications and reviews of ACT [Kalos, 2013; Klebanoff, 2016; Maus, 2014; Morgan, 2010; Robbins, 2011; Rosenberg, 2008].

The first observations that immune system engagement can lead to antitumor effects are often attributed to William Coley, who observed regression of sarcoma following severe bacterial infections in the 1890s. Further observations of the spontaneous regression of malignant melanoma lesions initially led to the use of T cells isolated from tumor-infiltrating lymphocytes (TILs). Cell therapy using tumor-reactive TILs has resulted in approximately 50% objective clinical regression in melanoma subjects [Dudley, 2005; Besser, 2010]. This therapy, however, has been limited by the requisite surgery to procure tumor-reactive TILs, by *ex vivo* identification and expansion of these cells (TILs could be generated from only 50% of resected samples), and by the failure to reproducibly isolate similar cells from other cancer types.

Adoptive transfer of bulk T lymphocytes, obtained from the periphery and expanded *ex vivo* to generate large numbers of cells prior to reinfusion into subjects, is an alternative strategy for ACT [Rapoport, 2005]. However, tumor cells are well known to be immunologically selected for low antigen presentation and the majority of tumor antigens are normally expressed self-antigens. Hence, the natural T-cell receptors (TCRs) that recognize self-tumor antigens may be of low affinity. The high tolerance to tumor antigens with normal and/or developmental expression combined with the potent immunosuppressive microenvironment often present at the tumor site is manifest in most cases by suboptimal activation in terms of antitumor activity such that "native" T cells may not be sufficient to induce tumor cell death in most subjects with advanced malignancy. Higher affinity TCRs allow T cells to respond to lower levels of antigen; this is important for tumor immunotherapy where the tumor microenvironment has adapted itself to reduce expression of antigen and also decrease expression of major histocompatibility complex (MHC) class I molecules [Marincola, 2000; Baccala, 2005; Barrett, 2009].

Gene-transfer-based strategies have therefore been developed to overcome the consequences of immune tolerance on the tumor-specific T-cell repertoire. These approaches provide the potential to redirect T cells to effectively target tumors by the transfer of antigen-specific affinity-optimized T-cell receptors. The majority of clinical approaches have employed T cells engineered to stably express transgenes via virus-based transduction. Virus-mediated gene transfer approaches typically employ vectors that are derived from gamma retroviruses or more recently lentiviruses.

Rational high-throughput genetic mutagenesis approaches have resulted in the ability to molecularly engineer TCRs with substantially higher affinities for target antigens. TCR-based engineering approaches have certain inherent biological advantages, most notably that essentially all cellular proteins can be targeted because the approach is not limited to the targeting of cell

surface epitopes, and the primary T-cell activation signal is delivered in a physiological context, which may be relevant for optimal functionality of the infused T cells. Additional details are provided in the current NY-ESO-1^{c259}T Investigators' Brochure (IB) for GSK3377794 [GSK Document Number 2018N369930_03].

1.2. Adoptive Immunotherapy with NY-ESO-1 (c259) Specific T Cells

NY-ESO-1 and LAGE-1a are members of the cancer-testis family of tumor antigens (CTAs). NY-ESO-1 gene expression was detected in 7-36% of multiple myeloma (MM) patients tested [Evans, 2001; van Baren, 1999] and has been shown to be highly expressed in poor prognosis MM [van Rhee, 2005].

LAGE-1 mRNA was detected in 49% of MM patients [Andrade, 2008] and its expression in relapsed MM cases has been associated with shorter progression-free survival (PFS) [van Duin, 2011]. LAGE-1a is among the genes whose expressions in MM patients have been shown to be correlated with resistance to proteasome inhibitor bortezomib [Richardson, 2003].

LAGE-1 encodes for two alternative splicing isoforms (a and b) and the corresponding encoded proteins are largely identical in the first 134 amino acids with 95% similarity between the two isoforms (LAGE-1a: 180 amino acids and LAGE-1b: 210 amino acids) [Matsui, 2008]. LAGE-1 amino acid sequence is also highly similar to NY-ESO-1 [Andrade, 2008]. Its expression has been frequently detected in a selection of MM patients, despite the notably lower expression of its close homologue NY-ESO-1. It has been suggested that because of the high sequence homology, LAGE-1 may also induce an immune response against NY-ESO-1. Moreover, the concomitant expression of LAGE-1 and NY-ESO-1 has been detected in 23% of the advanced stage MM patients [Condomines, 2007].

An HLA-A2 binding peptide (SLLMWITQC) corresponding to an amino acid sequence (157 to 165) that is common to both NY-ESO-1 and LAGE-1a antigens has been identified that can be recognized by NY-ESO-1 reactive T cells. NY-ESO-1 epitopes are also recognized in the context of multiple HLA class II restriction elements. Several studies have demonstrated antibodies against NY-ESO-1 in patients with cancer. NY-ESO-1 may be particularly immunogenic.

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

As of 27 January 2019, 100 subjects have received NY-ESO-1^{c259}T in (engineered using a lentiviral vector) in clinical trials in the indications of multiple myeloma, synovial sarcoma, melanoma, and ovarian cancer. A total of 27 of these subjects had MM; 25 were treated with NY-ESO-1^{c259}T in a post-transplant setting following myeloablative chemotherapy with high-dose melphalan and stem cell rescue [Rapoport, 2015]. The remaining 2 subjects were treated with NY-ESO-1^{c259}T with cyclophosphamide conditioning at a dose of 1500 mg/m^2 x 1 day. In the solid tumor (synovial sarcoma, melanoma, ovarian cancer) studies, the lymphodepleting regimens have consisted of cyclophosphamide with or without fludarabine. Refer to the NY-ESO-1^{c259}T IB [GSK Document Number 2018N369930_03] for further details.

1.3. Multiple Myeloma

MM is a cytogenetically heterogeneous clonal plasma cell proliferative disorder [Rajkumar, 2014]. It is characterized by several features as a result of the abnormal accumulation of myeloma cells within the bone marrow. These features include: skeletal destruction, bone marrow failure with resultant anemia, thrombocytopenia and neutropenia; increased plasma viscosity and impaired renal function due to the secretion of M protein from myeloma cells into the blood and urine; and suppression of normal immunoglobulin production.

The lifetime risk of getting MM is 1 in 143 (0.7%). The average annual incidence of MM is 3-4 per 100,000 persons representing 1.3% of all types of cancer. An estimated 32,110 people in the US will be diagnosed annually and an estimated 12,960 will die from the disease [American Cancer Society, 2019]. On a worldwide scale, it is estimated that about 86,000 incident cases of MM occur annually, accounting for about 0.8% of all new cancer cases [Becker, 2011]. About 63,000 subjects are reported to die from the disease each year, accounting for 0.9% of all cancer deaths. Geographically, the frequency is very unevenly distributed in the world with the highest incidence in the industrialized regions of Australia/New Zealand, Europe, and North America.

There have been multiple advances for the treatment of MM that have revolutionized the treatment of this disease leading to increase in survival. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) first introduced in the 1970s was shown in randomized trials versus chemotherapy to improve survival [Attal, 1996].

Although high-dose chemotherapy using alkylating agents such as melphalan followed by autologous hematopoietic cell transplantation (HCT) remains a core component of aggressive treatment armamentarium in younger and fit selected group of myeloma patients, relapse or progression of the underlying disease after autologous HCT and subsequent maintenance therapy remains inevitable [Palumbo, 2014; McCarthy, 2012; Attal, 2012]. Treatment strategies for MM have evolved over time from non-specific conventional combination chemotherapy approach to more biologically targeted therapies including proteasome inhibitors, immunomodulatory agents, histone deacetylase inhibitors and monoclonal antibodies against either myeloma or bone marrow microenvironment target antigens.

Immunomodulatory imide drugs (IMiDs, e.g., lenalidomide, pomalidomide) are approved for the treatment of patients with MM. Two randomized, double-blind, placebo-controlled studies compared lenalidomide/dexamethasone to dexamethasone alone in patients with relapsed or refractory multiple myeloma (RRMM) who had received at least one prior treatment

[Dimopoulos, 2007; Weber, 2007; Rajkumar, 2005; Zonder, 2007]. In the study by Dimopoulos et al, the median time to progression (TTP) was 11.3 months in the lenalidomide group and 4.7 months in the placebo group (P<.001). The hazard ratio for TTP was 2.85 (95% CI, 2.16-3.76; P<.001) in favor of the lenalidomide group. The median survival time in each study was similar and favored the combination arm [39.4 months (95% CI: 32.9, 47.4) lenalidomide/dexamethasone vs 31.6 months (95% CI: 24.1, 40.9) placebo/dexamethasone; 37.5 months (95% CI: 29.9, 46.6) lenalidomide/dexamethasone vs 30.8 months (95% CI: 23.5, 40.3) placebo/dexamethasone] [Revlimid USPI, 2015]. Similarly, a phase 2, randomized open-label study of pomalidomide/dexamethasone vs pomalidomide in patients with RRMM (had previously received lenalidomide and bortezomib), the efficacy favored the combination [Richardson, 2014]. The median PFS for the combination vs single agent pomalidomide was 4.2 and 2.7 months (HR = 0.68, 95% CI = 0.51-0.90, P = .003), overall response rates (ORRs) were 33% and 18% (P = .013), median response duration was 8.3 and 10.7 months, and median overall survival (OS) was 16.5 and 13.6 months (HR = 0.94, 95%, CI = 0.70-1.28, P = .709), respectively.

Proteasome inhibitors (e.g. bortezomib, carfilzomib) have also shown efficacy in subjects with RRMM. In a randomized study of bortezomib versus dexamethasone in subjects with progressive multiple myeloma following 1 to 3 prior therapies, the ORR for bortezomib treated subjects was 38% and median TTP was 6.2 months as compared to the ORR of 18% and median TTP of 3.5 months in the dexamethasone treated subjects [Richardson, 2005]. In a single arm Phase 2 study of carfilzomib in subjects who had received a median of 5 prior lines of therapy including bortezomib, lenalidomide, and thalidomide, the ORR was 23.7% with a median duration of response (DOR) of 7.8 months [Siegel, 2012]. The ORR of 52.2% was achieved when carfilzomib was given to subjects who were bortezomib naïve further supporting its activity in RRMM [Vij, 2012]. Further study of carfilzomib in combination therapy demonstrated the efficacy of carfilzomib plus lenalidomide and dexamethasone vs lenalidomide and dexamethasone for relapsed MM. PFS was significantly improved with the addition of carfilzomib: median PFS was 26.3 months, vs. 17.6 months in the lenalidomide+dexamethasone group (HR = 0.69; 95% CI = 0.57-0.83, P = .0001). 24-month OS rates were 73.3% and 65.0% in the carfilzomib+lenalidomide+dexamethasone and lenalidomide+ dexamethasone groups respectively (HR = 0.79; 95% CI = 0.63-0.99, P=.04). ORR was also improved to 87.1% with the addition of carfilzomib, vs. 66.7% in the dexamethasone +lenalidomide group (P<.001) [Stewart, 2015].

The HDAC inhibitor panobinostat has been approved in combination with bortezomib and dexamethasone, for the treatment of subjects with MM who have received at least 2 prior regimens, including bortezomib and an IMiD. A PFS advantage was shown in the panobinostat, bortezomib, and dexamethasone treated subjects compared with bortezomib and dexamethasone [12 months vs. 8.1 months; 0.63 (95% 0.52, 0.76); P < 0.0001] but the ORR did not differ (60.7% vs 54.6%) [San-Miguel, 2014]. In the final OS analysis the median OS in the panobinostat arm was 40.3 months and in the placebo arm 35.8 months (HR=0.94, 95% CI, 0.78-1.14, P=.5435) [Richardson, 2016].

Monoclonal antibodies such as elotuzumab (anti-SLAMF-7) and daratumumab (anti-CD38) are the most recently approved agents. A study of elotuzumab plus lenalidomide and dexamethasone vs. lenalidomide and dexamethasone alone showed an ORR of 79% and 1-year PFS of 68% in elotuzumab treated subjects compared to ORR of 66% and 1 year PFS of 57% for lenalidomide and dexamethasone alone [Lonial, 2015]. A single agent study of daratumumab in subjects with RRMM who had received at least 3 lines of therapy showed an ORR of 29.2% with a median DOR of 7.4 months [Lokhorst, 2015].

Exploratory approaches with chimeric antigen receptor (CAR-T) targeting the anti-B-cell maturation antigen (BCMA) have shown promising results in early phase clinical studies [Raje, 2019]. For example, bb2121 has been evaluated in patients who had received at least three previous lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or were refractory to both drug classes, with 85% ORR and median progression-free survival (PFS) of 11.8 months. Other promising BCMA-based immune-therapies, including bispecific T-cell engagers, bispecific molecules, bispecific or trispecific antibodies, as well as improved forms of next generation CAR T cells, also demonstrate high anti-multiple myeloma activity in preclinical and early clinical studies. Among these, a recent early phase study with the anti-BCMA antibody-drug conjugate (ADC) GSK2857916 showed preliminary results from 35 patients with relapsed or refractory multiple myeloma, who received the recommended dose of the drug [Trudel, 2019]. In this study, 21 (60.0%) of 35 patients achieved PR or better, including two sCR and three CR. The mPFS was 12 months and mDOR was 14.3 month.

Despite the number of therapies available to patients with RRMM, the majority of patients progress or relapse and die of their disease. New therapies are needed to further improve outcomes in this patient population.

1.4. NY-ESO-1^{c259}T in Multiple Myeloma

Twenty-five (25) subjects with MM received NY-ESO-1^{c259}T in the context of ASCT with melphalan as the conditioning regimen [study ADP-01411/NTC01352286]. The results on the first 20 MM subjects were reported [Rapoport, 2015]. All 25 subjects had active disease; 36% had undergone prior ASCT and 48% had high risk cytogenetic abnormalities (13q deletion, 17p deletion or >1 abnormality). The most common treatment-emergent, related adverse events (AEs) occurring in >20% of subjects were diarrhea, rash, pyrexia, and fatigue. Several subjects experienced a transient skin rash with lymphocytosis and others had a diarrheal syndrome that occurred later than expected for melphalan-induced mucositis, and which was later diagnosed as autologous graft versus host disease (aGVHD). Autologous GVHD has been reported in the post ASCT MM population and has been characterized by diarrhea, colitis, and rash. Liver chemistry elevations were low grade (Grade 1 or 2) and were of no clinical consequence. No bilirubin elevations have been observed. Most toxicities have occurred in the immediate post-treatment period (conditioning therapy and T-cell infusion) and usually resolved by Day 28 post-T-cell infusion. Other than fatigue, the vast majority of AEs resolved by Day 42.

Long-term follow-up including the analysis on the complete population of 25 enrolled MM subjects has now been reported [Rapoport, 2017]. T-cell expansion was detected in all subjects and persistence at Day 100 was observed in all but 1 subject. Clinical responses were observed

in 20 of 25 subjects (80%) with active disease, with 10 of 25 subjects (40%) having very good partial response (VGPR) or complete response (CR) or stringent complete response (sCR) by Year 1. The median PFS was 13.5 months (95% CI, 8.9-31.1), and the median OS was 35.1 months (95% CI, 22.7-NR). At study completion, 3 treated patients had remained disease progression-free for 60.6, 59.3, and 38.6 months, respectively.

1.5. Rationale for Combination of NY-ESO-1^{c259}T with Pembrolizumab for Multiple Myeloma

T cells are activated when the TCR binds specific antigen peptides presented by MHC on antigen presenting cells. Additional costimulatory signals through CD28 binding to B7-1 and B7-2 are essential for proliferation and effector function. The existence of a number of different immunosuppressive pathways can restrict the full potential of ACT. Increased expression of inhibitory immune receptors, such as PD-1, on T cells can limit the adaptive immune response. The physiologic role of PD-1 is to maintain T-cell homeostasis by limiting T-cell activation and proliferation by ligation of PD-L1 to PD-1 which transmits an inhibitory signal reducing cytokine production and limiting T-cell proliferation. PD-L1/PD-1 axis exerts its function as inhibitory mechanism counterbalancing the T-cell stimulatory signals. PD-1 is also involved in the maintenance of peripheral self-tolerance via suppression of autoreactive T cells.

Although PD-L1 is absent from normal plasma cells [Liu, 2007; Hallett, 2011] it has been shown to be present on myeloma cell lines and primary myeloma samples [Liu, 2007; Benson, 2010; Kuranda, 2010; Rosenblatt, 2011]. In a syngeneic PD-1 deficient mouse model, Iwai et al. first described that myeloma cell growth can be suppressed and also can be inhibited in normal syngeneic mice with an anti-PD-1 antibody [Iwai, 2002].

In a phase 1 study of single agent nivolumab (a fully human IgG4 monoclonal PD-1 receptor blocking antibody) in relapsed or refractory lymphoid malignancies, 27 subjects with MM were treated [Lesokhin, 2014]. There were no objective responses in the myeloma subjects with 67% stable disease rate. Nivolumab was given in a dose escalating design at 1 mg/kg and 3 mg/kg administered every 2 weeks up to 2 years.

San Miguel et al. reported the initial results of a phase 1 multicenter dose-escalation study of pembrolizumab (a humanized IgG4 anti-PD-1 monoclonal antibody) in 34 relapsed/refractory MM subjects (Keynote-023) with data on 17 subjects in the dose determination phase being provided in an abstract form [San Miguel, 2015]. Pembrolizumab was administered at 2 mg/kg to 200 mg/kg every 2 weeks in combination with 10 mg or 25 mg of lenalidomide on days 1-21 and 40 mg of dexamethasone weekly, to be repeated every 28 days. The objective response rate (ORR) was 76% with 4 of 17 subjects achieving very good partial response (VGPR) and 9 of 17 subjects achieving partial response (PR). ORR was observed in subjects with immunomodulatory-refractory and double-refractory disease [San Miguel, 2015].

These early results of anti-PD-1 antibody therapy especially in combination therapy are promising and many studies in MM using the strategy to target PD-1/PD-L1 axis are ongoing.

These results suggest that the combination of a targeted T-cell therapy with PD-1 blockage could result in improved efficacy.

1.5.1. Pembrolizumab Pharmaceutical and Therapeutic Background

Pembrolizumab [Keytruda USPI, 2020] is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the pembrolizumab IB [Pembrolizumab, 2019].

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the 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 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 Ig-variable–type (IgV type) 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, 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; and Riley, 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that

of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, 2005; Francisco, 2010].

Pembrolizumab has demonstrated initial clinical efficacy in combination with pomalidomide and dexamethasone in patients with relapsed/refractory myeloma and showed promising therapeutic activity [ORR was 50% in 11 of 22 evaluable subjects] and an acceptable safety profile in heavily treated RRMM patients [Badros, 2015].

Data from the on-going KEYNOTE-023 [Mateos, 2016] Phase 1 trial of pembrolizumab in combination with Revlimid and dexamethasone in patients with RRMM, has shown that of 40 patients evaluable for response, 50% responded, with 1 of 40 (3%) achieving a stringent complete response (sCR), 5 of 40 (13%) a VGPR, 14 of 40 (35%) a partial response. An additional 19 of 40 (48%) achieved stable disease, which is generally viewed as a positive outcome in later-stage patients. Among the patients who were refractory to Revlimid, 38% responded to combination therapy. With a median follow-up time of 9 months (range 1-25), the median DOR was 11.3 months and the median time to achieve the first objective response was 1.5 months (range 1.0-6.6). 75% of patients were still alive at time of clinical cut-off. The data also suggests that this treatment combination has an acceptable safety and tolerability profile that is consistent with AEs reported for pembrolizumab used in slide tumors.

Certain AEs observed with checkpoint inhibitors have been termed immune-related AEs (irAEs). Immune-related AEs reported with pembrolizumab include pneumonitis (~3%), enterocolitis (~1%), hepatitis (~0.5%), nephritis, rash, and endocrinopathies (hypothyroidism [7-8%], hyperthyroidism [1-2%], pancreatitis, adrenal insufficiency, hypopituitarism [0.2-0.5%]). Exfoliative dermatitis, rash, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and myasthenia gravis have been reported in less than 1% of patients.

Refer to the pembrolizumab IB and approved label for pembrolizumab for detailed background information [Pembrolizumab, 2019 and Keytruda USPI, 2020 respectively].

1.5.2. Rationale for the Pilot Study

In this 2-arm pilot study, the safety, tolerability, and antitumor activity of NY-ESO-1^{c259}T in subjects with RRMM in the context of a lymphodepleting preparative regimen of cyclophosphamide and fludarabine will be evaluated. Arm 1 will evaluate NY-ESO-1^{c259}T alone. The antitumor activity demonstrated in study ADP-01411/NTC01352286 was in the context of ASCT. Arm 1 of this study will assess antitumor activity of NY-ESO-1^{c259}T in a non-ASCT setting, isolating the efficacy and safety of NY-ESO-1^{c259}T alone in patients with RRMM.

Arm 2 will evaluate NY-ESO-1^{c259}T in combination with the PD-1 inhibitor pembrolizumab.

The immunomodulatory molecule PD-L1 is expressed on malignant plasma cells, myeloma-propagating pre-plasma cells and dendritic cells in the bone marrow of MM patients [Yousef, 2015; Sponaas, 2015]. However, single agent PD-1 inhibition has not yet proven to be effective

in treating patients with RRMM. The KEYNOTE-23 study early reports have already demonstrated the potential efficacy of combination therapy for these patients (see Section 1.5.1).

Additionally, PD-L1 expression on tumor cells and PD-1 on T cells can limit the adaptive immune response and promote resistance. Internal data on PBMC or BM samples collected at various time points, post-infusion, for the 25 patients from study ADP-01411/NTC01352286 show that CD8 T-cells that are either pentamer-positive or pentamer-negative (i.e. transduced or not respectively) express the exhaustion marker PD-1.

Therefore, the combination of NY-ESO-1^{c259}T and pembrolizumab could, not only result in an additive treatment effect from therapies with different mechanisms of action, but also may result in a synergistic effect due to the inhibition of PD-1 on the NY-ESO-1^{c259}T cells.

Preliminary safety and efficacy data on each individual component as well as the mechanistic rationale around the potential synergies support the investigation of this combination.

Recent early clinical studies using anti- BCMA regimens have shown promising results in the RRMM therapeutic setting. Patients who have failed anti-BCMA therapies may potentially benefit from receiving the NY-ESO-1^{c259}T cells because of the possible anti-tumor activity of targeting a non-redundant myeloma antigen [Raje, 2019; Trudel, 2019]. With this rationale, this study would include patients with RRMM in the post-BCMA failure setting [Timmers, 2019].

2. TRIAL OBJECTIVES AND ENDPOINTS

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To describe the safety and tolerability of autologous genetically modified T cells (NY-ESO-1^{c259}T) alone (Arm 1) or in combination with pembrolizumab (Arm 2) in subjects who are HLA-A*02:01, HLA A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 and/or LAGE-1a positive relapsed refractory multiple myeloma.	• Adverse events (treatment-limiting toxicities [TLT] and AEs), including serious adverse events (SAEs); laboratory assessments including chemistry, hematology and coagulation; and cardiac assessments by electrocardiogram (ECG).
Secondary	
• To evaluate the antitumor activity of autologous genetically modified T cells (NY ESO-1^{c259}T) alone (Arm 1) or in combination with pembrolizumab (Arm 2) in subjects who are HLA-A*02:01, HLA A*02:05, and/or HLA-A*02:06 positive and have NY-ESO-1 and/or LAGE-1a positive relapsed refractory multiple myeloma	• Overall response Rate (ORR) • Time to Response (TTR) • Duration of Response (DOR) for subjects who achieve at least PR • Progression-free survival (PFS)
• To describe the persistence of autologous genetically modified T cells (NY-ESO-1^{c259}T) over time	• Maximum persistence (Cmax), time to Cmax (Tmax), and area under the time curve from zero to time t AUC(0-t), as data permit

Objective	Endpoint
Exploratory	
• To describe the antitumor activity of autologous genetically modified T cells (NY-ESO-1^{c259}T) alone (Arm 1) or in combination with pembrolizumab (Arm 2) in subjects who are HLA A*02:01, HLA-A*02:05, and/or HLA A*02:06 positive and have NY ESO-1 and/or LAGE-1a positive relapsed refractory multiple myeloma.	• Overall survival (OS).
• To evaluate minimal residual disease (MRD) at 4 months post T-cell infusion (Week 15).	• MRD rate at Week 15.
• To evaluate the persistence, phenotype, and functionality of NY-ESO-1^{c259} positive T cells.	• Correlate persistence, phenotype, and functionality of NY ESO-1^{c259}T in the peripheral blood and/or bone marrow with response to treatment and safety.
• To understand mechanisms of resistance to NY-ESO-1^{c259}T.	• Determine whether loss of NY-ESO-1 and/or LAGE-1a expression in myeloma cells is a resistance mechanism. • Correlate apparition of anti-NY-ESO-1^{c259}T antibodies with efficacy and safety. • Correlate expression of PD-L1 in the tumor microenvironment and PD-1 expression on T cells with response to treatment. • Correlate frequency of immune cell subsets in peripheral blood and/or bone marrow with treatment response. • Correlate frequency of immune cell subsets in peripheral blood and in bone marrow.
• To evaluate antigen spreading as a mechanism of response.	• Correlate clonal outgrowth of T-cell populations with tumor response following T-cell infusion.
• To evaluate cytokine levels pre- and post-infusion on cytokine release syndrome (CRS).	• Correlate cytokine levels with incidence and severity of CRS or other safety events.
• To evaluate the impact of germline polymorphisms in IL-6, TNF-α, IL-10, INF-γ, and TGF-β on CRS.	• Polymorphisms in germline DNA will be correlated with CRS.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a pilot study of genetically engineered NY-ESO-1^{c259}T in HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 subjects with NY-ESO-1/LAGE-1a positive relapsed and refractory multiple myeloma (MM). Enrollment will continue in this study to ensure there are at least 10 subjects in each arm who have received treatment (with NY-ESO-1^{c259}T therapy for Arm 1 and, for Arm 2, NY-ESO-1^{c259}T therapy and pembrolizumab), with at least 6 treated subjects per arm who have previously received and failed a BCMA-based therapy (CAR-T, ADC, or other types

of BCMA-targeted therapies). Assignment to one of two arms will proceed as outlined below. Per Protocol Amendment 4, a total of at least ten subjects are to be enrolled into Arm 1 prior to restart of enrollment into Arm 2. Additional subjects may be enrolled if eligible subjects do not receive the NY-ESO-1^{c259}T infusion for Arm 1 or, for Arm 2, the NY-ESO-1^{c259}T infusion and pembrolizumab for any reason. It is anticipated that subject participation in this study will take approximately 42 months to complete (refer to Section 3.4). Figure 1 summarizes the subject flow in the study.

- Part 1 – Eligibility Screening: Subjects will sign the Screening Informed Consent Form and will be screened for the presence of HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 and for NY-ESO-1/LAGE-1a expression levels in the bone marrow (Section 3.2.1). Subjects who screen positive for the relevant HLA alleles and for the NY-ESO-1 and/or LAGE-1a tumor antigen(s) will sign the Treatment Informed Consent Form and enter the Eligibility Phase of the study.

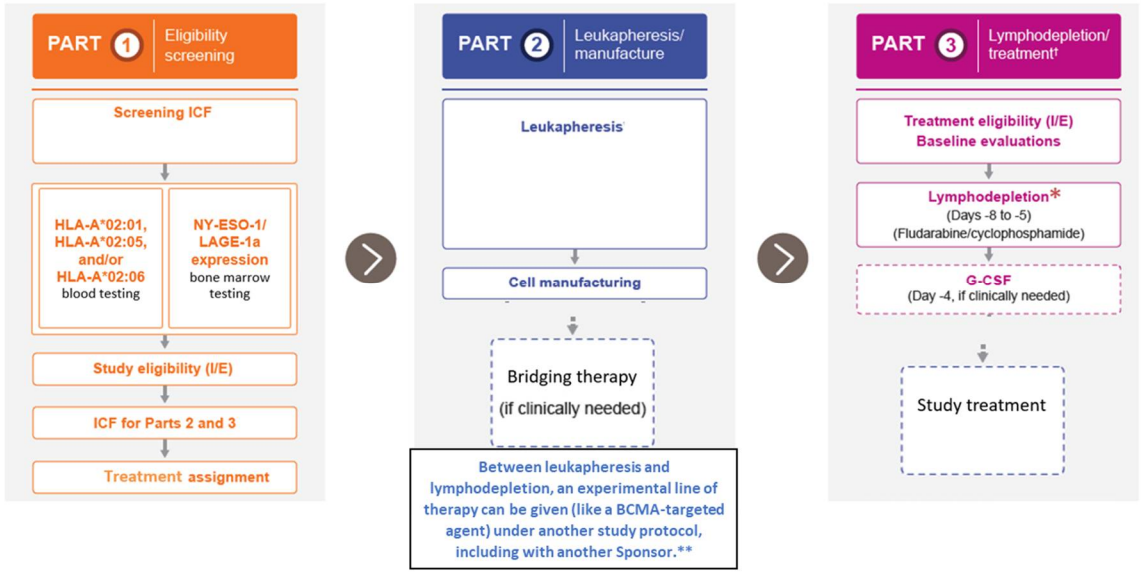
- Part 2 – Leukapheresis/Manufacture: If the subject meets the study eligibility criteria (Section 4), the subject begins the leukapheresis/manufacture part of the study. During this part, subjects can receive bridging therapy or a full line of another experimental regimen like a BCMA-targeted agent (Section 3.1.2.1 and Section 3.1.2.2).

  Note: A subject is considered to be enrolled once the subject has undergone leukapheresis.

- Part 3 – Lymphodepletion/Treatment: Once NY-ESO-1^{c259}T cells are released and the subject is eligible for the Treatment Phase of this study, lymphodepletion may begin, followed by NY-ESO-1^{c259}T-cell infusion. Part 3 runs from the first day of lymphodepletion until disease progression or 108 weeks after NY-ESO-1^{c259}T-cell infusion, whichever is sooner (completion of the Treatment Phase, see Section 4.2.2).

- NOTE: Subjects who complete the Treatment Phase will transfer to the Long-Term Follow-Up (LTFU) protocol (GSK208750 [ADP-0000-002]) to continue long-term safety monitoring of subjects. If the LTFU protocol is not available, subjects will be followed per the LTFU schedule of assessments detailed in Table 4 until the LTFU protocol becomes available.

Figure 1 Subject Flow



* For subjects aged ≥60 years, lymphodepleting chemotherapy doses can be adjusted after consulting with the sponsor, as per Section 5.2.1.

**Subjects receiving an experimental line of therapy between leukapheresis and lymphodepletion must have progressive disease from this intermediate line of therapy before receiving lymphodepletion in this study.

3.1.1. Part 1: Eligibility Screening

Subjects meeting all eligibility criteria will be assigned prior to leukapheresis into one of the 2 treatment Arms:

Arm 1: Subjects will receive NY-ESO-1^{c259}T alone as a single infusion.

Arm 2: Subjects will receive NY-ESO-1^{c259}T as a single infusion, in combination with pembrolizumab administered every 3 weeks. In Arm 2, 3 weeks after the infusion of NY-ESO-1^{c259}T on Day 1, an initial dose of pembrolizumab will be administered on Day 22 (Week 3). The second dose of pembrolizumab will be administered three (3) weeks later, at Week 6, and subsequent doses of pembrolizumab will be administered every 3 weeks thereafter up to Week 108 post T-cell infusion. If toxicities that preclude pembrolizumab treatment (such as CRS Grade ≥2) are observed at Day 22 (Week 3), infusion of pembrolizumab will start on Week 6. If toxicities have not resolved by Week 6, pembrolizumab will not be administered and the subject will be followed for visits as a subject in Arm 1.

Enrollment of Arm 1 will be completed before continuing enrolling subjects to Arm 2.

Anticancer therapy may be administered between screening and leukapheresis, if a subject has progressive disease and cannot be treatment-free. The appropriate wash-out period (17) prior to leukapheresis should be applied.

3.1.2. Part 2: Leukapheresis/Manufacture

Following assignment to either Arm 1 or 2, all subjects will undergo leukapheresis to obtain cells for the manufacture of autologous NY-ESO-1^{c259} bearing T cells. Leukapheresis should be performed as soon as possible after the subject is determined to be eligible for study participation and assigned to a treatment Arm.

3.1.2.1. Bridging Therapy

During Part 2, supportive therapy can be administered to “bridge” the subject to the treatment part of this study (Part 3).Anticancer therapy (bridging therapy), may be administered between leukapheresis and the start of lymphodepletion if a subject has progressive disease and cannot be treatment-free, but mandatory washout periods (see exclusion criterion 21) must be respected.

Bridging therapy may consist of an experimental regimen under another study protocol, including with another Sponsor.

Adverse event collection for subjects receiving bridging therapy is described in Section 9.1

3.1.2.2. Intermediate Line of Therapy

Between leukapheresis and lymphodepletion, an experimental line of therapy may be given (such as a BCMA-targeted agent) under another study protocol, including with another Sponsor. In this

case, subjects receiving an experimental line of therapy between leukapheresis and lymphodepletion must have progressive disease from this intermediate line of therapy before receiving lymphodepletion in Study 208470.

3.1.3. Part 3: Lymphodepletion/Treatment

The subject must begin lymphodepletion within two years after leukapheresis.

Less than or equal to 7 days before initiating the lymphodepleting chemotherapy, baseline eligibility criteria will be re-confirmed, and baseline multiple myeloma tumor assessment obtained. Once the manufactured NY-ESO-1^{c259}T product has been received and the integrity of the bag(s) has been verified by the site, each subject will undergo lymphodepletion with cyclophosphamide and fludarabine (Section 5.2) in preparation for infusion of NY-ESO-1^{c259}T on Day 1 (Section 5.3). Subjects will receive Granulocyte-Colony Stimulating Factor (G-CSF) support starting 24 hours after lymphodepleting chemotherapy. Refer to Section 8 for supportive care guidance on T-cell infusion.

For subjects treated in Arm 2 with pembrolizumab (200 mg IV, every 3 weeks), the initial dose of pembrolizumab will be administered on Week 3 (on Day 22, 21 days after the T-cell infusion on Day 1). The second dose of pembrolizumab will be administered three (3) weeks later, at Week 6, and subsequent doses of pembrolizumab will be administered every 3 weeks thereafter up to Week 108 post T-cell infusion. If toxicities that preclude pembrolizumab treatment (such as CRS Grade ≥2) are observed at Day 22 (Week 3), infusion of pembrolizumab will start on Week 6. If toxicities have not resolved by Week 6, pembrolizumab will not be administered and the subject will be followed for visits as a subject in Arm 1.

Subjects will be frequently monitored for any unexpected ≥Grade 3 AE and any SAE; subjects treated in the combination Arm 2 will also be monitored for TLTs as outlined in Section 3.3.5.

Efficacy, safety, and biomarker assessments to be conducted at each visit are outlined in the Schedule of Procedures (Table 3). The efficacy will be assessed using the International Myeloma Working Group (IMWG) Response Criteria [Kumar, 2016].

Subjects will complete the Treatment Phase of the study upon diagnosis of their disease progression or 108 weeks after NY-ESO-1^{c259} T-cell infusion, whichever is sooner (refer to Figure 1). If disease progression occurred prior to the Week 12 visit, subjects should remain on the treatment phase schedule to ensure collection of safety following T-cell infusion for a minimum of 9 weeks.

All subjects will ultimately enter a LTFU protocol once they meet one of the criteria for the transfer (Section 4.4).

Passage to the Long-Term Follow-Up (LTFU) Study

Subjects will be followed for observation of delayed AEs for up to 15 years from the time of the T-cell infusion in accordance with FDA [FDA, 2020] and EMA [EMA, 2009] requirements for gene therapy clinical trials. All subjects will continue to be followed for OS during the LTFU phase.

3.2. Rationale for Components of Study Design

3.2.1. Screening for HLA and for expression of NY-ESO-1 and LAGE-1a antigens in the Context of NY-ESO-1^{c259}T

The prevalence of HLA sub-types varies from population to population, the most common in the Western world being HLA-A*02, thus HLA-A*02 is extensively studied structurally and functionally.

The NY-ESO-1^{c259}T specifically recognizes the HLA-A*02:01, HLA-A*02:05, and HLA-A*02:06-restricted NY-ESO-1/LAGE-1a peptide antigen HLA-A*02-SLLMWITQC; therefore, this protocol will select for subjects with these three most common HLA-A*02 allelic variants. Further information on prevalence is available at www.allelefrequencies.net. It is recommended that Investigators review the database for HLA-A2 allelic variants relevant to the study population at their site.

3.2.2. T-cell Manufacturing

NY-ESO-1^{c259}T is one of the two Investigational Products (IPs) in this study; NY-ESO-1^{c259}T is comprised of autologous CD4 and CD8 T cells that have been transduced with a self-inactivating (SIN) lentiviral vector expressing an affinity enhanced NY-ESO-1/LAGE-1a specific TCR. The product of this transduction is polyclonal T cells which are designed to target NY-ESO-1/LAGE-1a in tissue. The transfer vector is a SIN lentiviral vector which has been meticulously designed to contain only the minimal genetic elements required for function, and no vector proteins for maximum biosafety [Dull, 1998]. Lentiviral vectors are a subset of retroviral vectors thought to have an enhanced safety profile. Many reports provide evidence supporting the relative biosafety of SIN lentiviral vectors in terms of genotoxicity, resulting primarily from the lack of enhancer activity in the lentivirus long terminal repeat (LTR) in comparison to the γ retroviral vectors [Montini, 2006; Maruggi, 2009; Modlich, 2009; Montini, 2009].

Selected qualified manufacturing sites will prepare NY-ESO-1^{c259}T for subjects enrolled at all sites. Utilizing anti-CD3/CD28 monoclonal antibody (mAb) coated magnetic beads, T cells are enriched, activated and expanded (for at least 13 days). Cell product typically is ready to be returned to the site within less than three months after subject apheresis and will be available for shipment approximately one week prior to the scheduled infusion and before the start of chemotherapy.

After the *ex vivo* activation and expansion, the final cellular product is typically >90% T lymphocytes since the culture conditions do not support the growth of macrophages, natural killer (NK) or B cells. By the end of the culture period, B cells comprise approximately <2%, NK cells approximately <2%, and macrophages approximately <1% of the total culture. Additional details are provided in the NY-ESO-1^{c259}T IB [GSK Document Number 2018N369930_03].

3.2.3. Lymphodepletion

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] and facilitate trafficking of the engineered T cells [Pinthus, 2004]. Lymphodepletion also enhances the activity of the adoptively transferred cells via the removal of inhibitory factors such as regulatory T cells [Wolf, 2003] and can activate antigen presenting cells through the induction of inflammatory cytokines and induction of tumor apoptosis with resulting cross presentation of tumor antigens to T cells.

Recent evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy depends not just on the depth of cytoreduction but additionally on the specific action of some cytotoxic drugs. Recent studies in lymphoma, chronic leukemia, and acute leukemia using adoptive cellular therapy including a chimeric antigen receptor showed increased T-cell expansion, persistence, and disease-free survival when fludarabine was added to a previously cyclophosphamide-only preparative regimen [Turtle, 2016].

Based on the results from our previous clinical research using combination fludarabine-cyclophosphamide lymphodepleting chemotherapy and the increasing evidence that fludarabine may be a necessary component, the lymphodepleting regimen in this study consists of fludarabine 30 mg/m^2/day and cyclophosphamide 900 mg/m^2/day intravenously for 4 and 3 consecutive days, respectively (see dose modification for patients over 60 years of age in Section 5.2).

3.2.4. T-Cell Infusion

One of the IPs in this study is the infusion of autologous T cells transduced with lentivirus encoding enhanced TCR specific for NY-ESO-1^{c259}T (see Section 5.3 for administration details).

3.2.5. Rationale for NY-ESO-1^{c259}T Dose

Activity of NY-ESO-1^{c259}T seems to be indirectly related to dose administered (depending also on cell expansion and persistence). Total T-cell doses up to ~100 × 10^9 cells (median of 5 × 10^{10} transduced T cells with an anti-NY-ESO-1 TCR range of 1.6 to 130 ×10^9) [Robbins, 2011] have been used although the actual products may differ depending on manufacturing methods.

Conversely, doses of CAR-T cells as low as 1.5×10^5 CD19 may also be effective [Porter, 2011].

Current experience with NY-ESO-1^{c259}T (n=100 subjects treated as of January 2019) is with total cell doses in the range of 0.4×10^9 to 3.47×10^{10} with a transduction level of ~18 to 75% (transduced cell dose range of 0.23×10^9 to 14.36×10^9). No identifiable increase in AEs has been observed in subjects who received higher transduced cell doses ($>5 \times 10^9$ cells). Of the 5 subjects who received $<1 \times 10^9$ transduced cells, 3 subjects had poor expansion and persistence of transduced cells; meaningful clinical responses were not observed in 4 of the 5 subjects. No clear dose response relationship has been observed to-date.

Based on this data, a range of 1×10^9 to 8×10^9 transduced cells will be administered by a single intravenous (IV) infusion on Day 1. If the transduced cell dose is less than the minimum dose of 1×10^9, 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.

3.2.6. Rationale for Pembrolizumab Dose and Timing of the First Dose

3.2.6.1. Rationale for Pembrolizumab Dose

Pembrolizumab is the other IP in this study and will only be given to subjects in Arm 2. The dose of pembrolizumab planned to be studied in this trial is 200 mg administered Q3W from Week 3 (or Week 6) until Week 108.

Based on the totality of data generated in the Keytruda development program, 200 mg every three weeks (Q3W) is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, 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 OS 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 subjects were enrolled with melanoma and non-small cell lung cancer (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 subject 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.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

3.2.6.2. Rationale for Timing of First Dose

Timing of the first dose of pembrolizumab takes into account the mechanism of action of both agents as well as their safety profiles. The lymphocyte nadir induced by the lymphodepleting chemotherapy coincides with the NY-ESO-1^{c259}T-cell infusion at study Day 1. As T cells expand, they express exhaustion markers including PD-1 (internal data) therefore pembrolizumab should be administered when the AEs of lymphodepleting chemotherapy and T-cell infusion have begun to subside and expanding PD-1 expressing T-cells are present. The contraction phase of the T cells begins by Week 3, however there is persistence of the PD-1 expressing transduced NY-ESO-1^{c259}T cells at this point in time. A review of the treatment-emergent toxicities in the first 53 patients treated with NY-ESO-1^{c259}T in GSK clinical trials shows that while 41 of 53 (77%) subjects experienced ≥Grade 2 AEs in the first week post T-cell infusion, these AEs resolved to an acceptable level by Week 3 and that only one (1) subject (2%) has experienced a Grade 2 AE of elevated alanine aminotransferase (ALT) that would have precluded from receiving the first dose of pembrolizumab at Week 3.

The first dose of pembrolizumab in this study will be given 3 weeks after T-cell infusion (Day 22). The separation of the T-cell infusion and the first dose of pembrolizumab will allow for the checkpoint inhibitor administration when PD-1 expressing T cells persist while minimizing the potential for overlapping toxicities.

3.3. Assessment of Safety and Treatment Limiting Toxicities

Safety will be assessed in a continuous manner (See Section 8 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). Refer to Section 10.3 for a description of the SRT.

Safety data will be proactively reviewed for each subject and/or summarized by subject and in aggregate across subjects by arm. The toxicities observed will be reviewed in the context of the known safety profiles of NY-ESO-1^{c259}T and pembrolizumab.

Most toxicities associated with lymphodepleting chemotherapy and NY-ESO-1^{c259}T occur in the first 4 weeks of therapy. Resolution of these toxicities is generally observed by Week 4 post T-cell infusion (approximately 5 weeks after the initiation of lymphodepleting chemotherapy). Toxicities associated with pembrolizumab have variable times to onset. When pembrolizumab is administered with NY-ESO-1^{c259}T, it is expected that the checkpoint blockade will activate the immune system. This could lead to enhanced antitumor activity as well as toxicity, hence, the pause of enrollment in Arm 2 combination arm described in Section 3.3.1 below.

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, graft versus host disease (GVHD), cytokine release syndrome (CRS), secondary pancytopenia, pneumonitis, endocrinopathies, nephritis, and any other manifestations that may indicate an immune-related phenomenon.

Additional criteria for possible suspension of treatment/enrollment are also provided in Section 4.7.

3.3.1. Pause of Enrollment in Arm 2 After the Third Subject in Arm 2 Begins Lymphodepletion

Study enrollment to Arm 2 will be paused after the third subject enrolled in Arm 2 has started lymphodepletion, in order to allow for a complete safety review to be conducted by the Sponsor and the SRT, and before a decision to resume enrollment in Arm 2 can be made (see Section 3.3.3 for the scope and timing of the safety review).

If one or more of the first three (3) subjects who receive lymphodepletion in Arm 2 fails to receive NY-ESO-1^{c259}T or fails to initiate pembrolizumab by Week 6 due to unresolved

toxicities, the enrollment may be re-opened temporarily and paused again each time a new subject begins lymphodepletion in Arm 2. This will ensure accrual of the 3 subjects needed for the initial safety evaluation (3 subjects treated with NY-ESO-1^{c259}T and who have initiated pembrolizumab), without over enrolling prior to the conclusion of the complete safety review of the first 3 subjects. Per Section 3.3.4, the SRT may recommend that enrollment should not be temporarily re-opened before the safety evaluation is complete. If more than 3 subjects enrolled in Arm 2 are apheresed and have cells manufactured before completion of the evaluation, the SRT will determine in terms of benefit:risk if the safety data available at the time supports proceeding with treatment of any of the additional subjects while the data from the first 3 subjects treated is being reviewed.

3.3.2. Scope of Reviews by the SRT

All serious adverse events (SAEs) and AEs ≥Grade 3 will be reviewed for both arms.

This is the first time NY-ESO-1^{c259}T is being administered in combination with pembrolizumab. To ensure that the toxicities observed with the combination are consistent with the known safety profiles of each individual therapy not only in terms of their type, but also of their incidence and their severity, subjects in Arm 2 will additionally be monitored for:

- treatment limiting toxicities as defined in Section 3.3.5
- any AE that led to treatment discontinuation of pembrolizumab

After the first 3 subjects on Arm 2 who have been dosed with NY-ESO-1^{c259}T and initiated pembrolizumab with at least 3 weeks of follow-up after the first dose, a complete safety review will be conducted (see Section 3.3.3). During this review and from that point on, considerations should also be given by the SRT to the clinical/statistical guidance in Section 11.4.1.2.

3.3.3. Complete Safety Review before Resuming Enrollment

The complete safety review will require TLT assessment of the first three (3) subjects assigned to Arm 2 who have been infused with NY-ESO-1^{c259}T, received their first dose of pembrolizumab and cleared the TLT 3-week assessment period.

3.3.4. Frequency of SRT meetings

SRT will meet to conduct the safety review described in Section 3.3.3; meeting frequency will be determined in the SRT charter.

The SRT may at any time recommend pausing/delaying/stopping/resuming enrollment in either arm of the study.

3.3.5. Treatment Limiting Toxicities (TLTs)

3.3.5.1. Three-Week Assessment Period

To evaluate the feasibility of the combination in Arm 2, TLTs will be assessed for the 3-week period as follows:

- from Week 3-Week 6 for subjects who initiated pembrolizumab on Week 3, or
- from Week 6-Week 9 for subjects who initiated pembrolizumab on Week 6.
- from Week 3-Week 6 for subjects who have been permanently precluded from initiating pembrolizumab due to unresolved toxicities after 6 weeks post T-cell infusion.

3.3.5.2. TLT Definition

- The following toxicities are considered to be TLTs:

  - Any ≥ Grade 4 AE except for the exclusions listed below.
  - Grade 3 non-infectious pneumonitis.
  - Any other Grade 3 AE (excluding pneumonitis), 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, lymphopenia, neutropenia, or febrile neutropenia;
  - Grade 3 or 4 thrombocytopenia not associated with significant bleeding;
  - Grade 3 anemia;
  - Grade 4 cytokine release syndrome (CRS) or toxicities related to CRS resolving to Grade ≤ 2 within 7 days;
  - Other 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 that prevents dosing of pembrolizumab at Week 3, has not resolved to acceptable level by Week 6, and consequently precludes a subject assigned to Arm 2 from initiating pembrolizumab will be counted as a TLT.

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

3.4. Number of Subjects and Duration of Study

Enrollment will continue in this study to ensure there are at least 10 subjects in each arm who have received treatment (with NY-ESO-1^{c259}T therapy for Arm 1, and, for Arm 2, NY-ESO-1^{c259}T therapy and pembrolizumab), with at least 6 treated subjects per arm who have previously received and failed a BCMA-based therapy (CAR-T, ADC, or other types of BCMA-targeted therapies). For these post-BCMA subjects, BCMA-targeted therapies may have been received prior to enrollment in this study or as an intermediate line of therapy between leukapheresis and lymphodepletion while on this study.

If 10 subjects have been enrolled into Arm 1 but fewer than 6 of those 10 subjects have or will receive some type of BCMA therapy, then any eligible subject who has or will receive BCMA therapy will be enrolled into Arm 1 until the target enrollment of 6 post-BCMA subjects in Arm 1 has been reached. Until enrollment into Arm 1 is complete, subjects who have not or will not receive any BCMA therapy will be enrolled into Arm 2.

Once at least 10 subjects overall and at least 6 post-BCMA subjects have been enrolled into Arm 1, then all subsequent subjects regardless of BCMA therapy status will be enrolled into Arm 2.

In both arms, subjects who do not receive NY-ESO-1^{c259}T therapy may be replaced.

In Arm 2, in case of subjects who do not receive pembrolizumab (perhaps due to incompatible toxicity after NY-ESO-1^{c259}T-cell infusion), enrollment may be further extended to ensure at least 10 subjects will receive pembrolizumab.

It is assumed that approximately 20% of the subjects will discontinue from the study prior to NY-ESO-1^{c259}T cell infusion.

Study enrollment is expected to require approximately 18 months. It is anticipated that the final analysis would be conducted approximately 24 months after the last subject has been enrolled, or shortly after the last subject has disease progression, whichever is sooner. The study will be considered complete once the last enrolled subject has transitioned to the LTFU protocol GSK208750 (ADP-0000-002).

3.5. Sites

The protocol will be conducted in approximately 10 sites in North America and Europe. The number of centers is necessary to ensure recruitment in this targeted population. Additional centers may be added at the discretion of the Sponsor.

3.6. Benefit:Risk Assessment

The results of Clinical and Non-Clinical studies conducted with NY-ESO-1^{c259}T are summarized in the IB [GSK Document Number 2018N369930_03]. Similarly, results of studies conducted with pembrolizumab are summarized in the pembrolizumab IB [Pembrolizumab, 2019]. It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during

participation as these studies are designed to provide information about the safety and effectiveness of investigational medicines. This section outlines the potential benefits, risks and the mitigation strategy for this study.

3.6.1. Benefit Assessment

NY-ESO-1 and LAGE-1a are highly expressed (based on gene expression profiling) in patients with MM. Increased expression of NY-ESO-1 antigen has been observed in patients with cytogenetic abnormalities compared to those with normal cytogenetics (60% versus 31%, *P*=.004) and in relapsing patients especially those with cytogenetic abnormalities (100% relapsing patients versus approximately 60% at diagnosis, *P* <.001) [van Rhee, 2005]. NY-ESO-1 and LAGE-1a antigens are ideal tumor targets for immunotherapies.

This clinical trial is designed to evaluate the safety, tolerability and antitumor activity of NY-ESO-1^{c259}T in subjects with RRMM whose tumors express NY-ESO-1 and/or LAGE-1a. Despite the many advances in treatment for MM, including promising clinical data from early studies testing anti-BCMA targeted therapies in RRMM [Raje,2019; Trudel, 2019], patients with RRMM ultimately die from their disease and more effective therapies are needed. In this study, enrollment is allowed to subjects who have received and failed an anti-BCMA targeted therapy. These subjects may potentially benefit from receiving the NY-ESO-1^{c259}T cells because of the possible anti-tumor activity of targeting a non-redundant myeloma antigen [Timmers, 2019]. Safety and antitumor activity of NY-ESO-1^{c259}T in patients with multiple myeloma has been demonstrated in the context of ASCT [Rapoport, 2015]. Twenty-five (25) subjects with MM have received NY-ESO-1^{c259}T in conjunction with ASCT on study ADP-01411/NTC01352286. Clinical responses for this group were observed in 16 of the first 20 myeloma subjects (80%) with active disease, with 14 of 20 subjects (70%) having near complete response (nCR) or CR by Day 100 [Rapoport, 2015]. At final analysis, three patients remained disease progression-free at 38.6, 59.2, and 60.6 months post-NY-ESO-1^{c259}T. Median progression-free survival was 13.5 months (range, 3.2-60.6 months); median overall survival was 35.1 months (range, 6.4-66.7 months) [Stadtmauer, 2019].

Pembrolizumab is a potent and highly selective humanized anti–PD-1 monoclonal antibody that directly blocks the interaction between PD-1 and its ligands. Pembrolizumab is approved for advanced melanoma and non–small cell lung cancer and has demonstrated robust antitumor activity in multiple cancers.

As a single agent, anti-PD-1 antibodies have shown minimal activity in relapsed MM: nivolumab alone could only demonstrate a stable disease rate of 67 percent in a phase I trial; partial responses or better were not seen [Lesokhin, 2014]. However, high response rates have been observed when anti–PD-1 antibodies and IMiDs are used in combination. Preliminary findings from the phase I KEYNOTE-023 (NCT02036502) [San Miguel, 2015] study of pembrolizumab in combination with the established lenalidomide+dexamethasone regimen (ORR 76%, median DOR 9.7 months) and early reports of a phase II study combining pembrolizumab with pomalidomide (Pomalyst) and dexamethasone (NCT02289222) [Badros, 2015] (ORR 60%, 75% PFS at 6 months) both show early signs of activity in heavily pretreated patients with MM.

This evidence supports the potential therapeutic benefit of NY-ESO-1^{c259}T in combination with pembrolizumab in patients with MM.

3.6.2. Risk Assessment

The known safety profile of GSK3377794 is based on 119 enrolled and 100 treated subjects as of 27 January 2019 (IB [GSK Document Number 2018N369930_03]). The most commonly reported treatment-emergent adverse events which occurred in ≥50% of subjects following GSK3377794 infusion were nausea (82%), anemia (79%), neutropenia (79%), leukopenia (78%), thrombocytopenia (75%), pyrexia (73%), fatigue (72%), diarrhoea (58%) and lymphopenia (50%). The most common Grade 3 and 4 AEs which occurred in ≥50% of subjects following lymphodepleting chemotherapy and GSK3377794 infusion were leukopenia (76%), neutropenia (71%), thrombocytopenia (60%), and anemia (57%). These AEs are consistent with expected immediate adverse events after lymphodepletion chemotherapy.

Across all studies, 34 (34%) subjects had SAEs considered by the Investigator to be related to study treatment. The most common treatment-related SAEs were: CRS (12%), pyrexia (7%), febrile neutropenia (3%), neutropenia (3%), rash (3%), dehydration (2%), diarrhea (2%), Guillain-Barré syndrome (2%), hypotension (2%), thrombocytopenia (2%), and unspecified GvHD (2%). For the 15 subjects who received a second infusion, five treatment related SAEs were reported after second T-cell infusion, which included 1 case each of CRS, cytomegalovirus infection, thromboembolism, febrile neutropenia, and rash.

Among the adverse events of special interest,

1. CRS was reported in 29 cases (of 100) as of 27 January 2019 across all GSK3377794 clinical trials. Of these, there was 1 subject with Grade 4, 6 with Grade 3, 11 with Grade 2, and 11 with Grade 1. Five cases were treated with tocilizumab. Median duration of the CRS events was 8 (after first infusion) and 9 days (after second infusion (range across first or second infusion 2-28 days).
2. A total of 7 cases (of 100) of GvHD have been reported of which 3 cases were reported as an SAE. All cases were Grade 1-3, occurred in patients with multiple myeloma, and completely recovered with supportive treatment. Six (6) out of 7 subjects with reported GvHD were from Study 209393 (formerly ADP-01411) which required an allogeneic stem cell transplant prior to the T-cell infusion.
3. Encephalopathy was reported in 1 case with multiple brain metastasis, that was transient, and resolved in 2 days with supportive care.
4. Five (5%) subjects had reported treatment-emergent AE of pancytopenia (3 subjects: 2 with Grade 3, and 1 with Grade 1) or bone marrow failure (2 subjects: 1 with Grade 5 fatal, and 1 with Grade 2) (refer to IB [GSK Document Number 2018N369930_03] for details).
5. Guillain Barre Syndrome (GBS) has been reported in 2 subjects, both of which completely recovered with standard gamma globulin treatment

To date, none of the analyses for Insertional oncogenesis and Replication competent lentivirus are positive for insertional oncogenesis or replication competent lentivirus. The potential risks of replication competent lentivirus (RCL) and insertional oncogenesis are being monitored in accordance with FDA guidance [FDA, 2006]. With the advent of replication incompetent lentivirus and the use of fully differentiated human T cells, there have not been any oncogenic integration events reported in any patient treated with T-cell gene therapy.
To date, on all samples assessed for evidence of insertional oncogenesis and replication competent lentivirus, the reported findings have been negative.

For those subjects who are enrolled in Study 208470 after having failed other gene and cell therapies (e.g. anti-BCMA CAR-T cell treatment) the risk of insertional oncogenesis following two separate gene transduction events using lentivirus technologies is nonetheless, considered extremely unlikely.

Guidance for the management of CRS, GVHD and pancytopenia with bone marrow failure following initial bone marrow recovery is provided in the protocol. The guidance is based on published literature (see Section 8). There are no published treatment guidelines for autologous GVHD, therefore guidance for treatment of allogeneic GVHD is used. Study sites are expected to have access to physicians with expertise in bone marrow transplant, and infectious diseases for consultation in the event of a subject developing either CRS or GVHD-like symptomatology. Electronic case report forms have been created to specifically capture information on these toxicities.

GSK are also monitoring reports of recurrent pancytopenia after initial bone marrow recovery following lymphodepleting chemotherapy and NY-ESO-1^{c259}T-cell infusion. In order to manage this risk, the Sponsor have developed standard protocol guidance on the management of pancytopenia with bone marrow failure following initial bone marrow recovery. Management of bone marrow failure (aplastic anemia) and related cytopenias is challenging, with no clearly established guidelines regarding immunosuppression. Therefore, treatment is largely supportive, including transfusions and treatment of infections. Guidance includes a recommendation to consult with physicians with expertise in the management of aplastic anemia and infectious diseases.

The goal of the risk management measures is to maximize the chance of therapeutic benefit while mitigating and better understanding the risks of treatment with NY-ESO-1^{c259}T-cell therapy.

The overall safety profile of pembrolizumab is derived primarily from the Merck's Reference Safety Dataset (RSD) (n=2799) which is a locked and verified dataset with pooled data from monotherapy clinical trials in melanoma and NSCLC. The majority of subjects, 2727 or 97.4%, experienced 1 or more AEs, and 2062 (73.7%) experienced 1 or more AEs reported as drug-related by the investigator. The percentage of subjects who experienced SAEs was lower; 1042 (37.2%) of subjects experienced 1 or more SAEs; 334 (11.9%) subjects discontinued due to an AE, and 282 (10.1%) subjects experienced a drug-related SAE, as determined by the investigator. The 5 most frequently reported AEs were: fatigue (37.3%), nausea (24.5%),

decreased appetite (22.5%), diarrhea (22.3%), and cough (22%). The 5 most frequently reported SAEs were pneumonia (3.0%), pleural effusion (1.7%), pneumonitis (1.6%), dyspnea (1.6%) and pulmonary embolism (1.5%). The 5 most frequently reported AEs considered drug related by the investigator were fatigue (24.2%), pruritus (16.7%), rash (13.8%), diarrhea (12.3%), and nausea (10.9%). The 5 most frequently reported SAEs considered drug-related by the investigator were pneumonitis (1.6%), colitis (0.9%), diarrhea (0.6%), pyrexia (0.4%), and autoimmune hepatitis, pneumonia, adrenal insufficiency, and hyponatremia, all reported at an incidence of (0.3%). Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%). Furthermore, the frequency of immune-mediated AEs is low, and these events are readily managed in the clinical setting.

Patients who receive allo-SCT following treatment with checkpoint inhibitors may be at increased risk for certain adverse effects including GVHD, veno-occlusive disease, febrile syndrome, and encephalitis.

Multiple myeloma is not an approved indication for pembrolizumab but numerous studies in patients with multiple myeloma are ongoing. Toxicity profile of pembrolizumab in multiple myeloma patients observed so far had been similar to studies in other tumor types, but important safety and efficacy information have now been reported on 2 Merck-sponsored trials that combined (1) pembrolizumab with pomalidomide and dexamethasone (KN183, NCT02576977) in subjects with refractory or relapsed and refractory multiple myeloma and (2) pembrolizumab with lenalidomide and dexamethasone (KN185, NCT02579863) in subjects with newly diagnosed and treatment naïve multiple myeloma. The US FDA placed studies KN183, KN185 and a cohort of KN023 (subjects with refractory or relapsed and refractory multiple myeloma on pembrolizumab+lenalidomide+dexamethasone) on full clinical hold based on an excess number of deaths in the investigational arms of both KN183 and KN185. For KN183 the OS HR of the pembrolizumab containing investigational arm compared to the control arm was 1.61 (95% CI: 0.91, 2.85), increasing the relative risk of death by more than 50% compared to the control arm. In KN185, the OS HR of the pembrolizumab-containing investigational arm compared to the control arm was 2.06 (95% CI: 0.93, 4.55), more than doubling the relative risk of death compared to the control arm. These studies are closed due to the unfavorable benefit-risk profile for the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma, and the combination of pembrolizumab, lenalidomide, and dexamethasone in newly diagnosed treatment -naive multiple myeloma [Mateos, 2019; Usmani, 2019].. While these studies that combine IMiDs with pembrolizumab have been stopped for safety reasons, other studies investigating the use of pembrolizumab in combination with other treatments for MM are ongoing. IMiDs will not be used in this combination study.

The potential risk of the combination of NY-ESO-1^{c259}T-cell therapy and pembrolizumab will be carefully monitored through a frequent follow-up visit schedule, pause of enrollment after the first three (3) subjects treated with the combination, and monitoring of all AEs.

3.6.3. Overall Benefit: Risk Conclusion

Data from preclinical studies support the specificity and safety of NY-ESO-1^{c259}T cells (IB [GSK Document Number 2018N369930_03]). Data from the clinical trial ADP-01411/NTC01352286 [Rapoport, 2015] demonstrate the safety and antitumor activity of NY-ESO-1^{c259}T in patients with MM sufficiently to support further clinical investigation of this product in MM. Based on the potentially complimentary mechanisms of action of NY-ESO-1^{c259}T cells and pembrolizumab, and the ongoing unmet need for better therapies for patients with RRMM, including those cases of subjects in the post-BCMA setting, the overall benefit:risk of this combination supports an initial clinical study. Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying informed consent documents.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Subjects will be assessed for and must meet eligibility for study participation prior to leukapheresis AND prior to lymphodepleting chemotherapy.

4.1. Subject Inclusion Criteria

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

4.1.1. Screening (Part 1)

1. Subject has voluntarily agreed to participate by giving written informed consent for the screening process in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and applicable local regulations.
2. Subject has voluntarily agreed to abide by all protocol required procedures including study related assessments, and management by the treating institution for the duration of the study and long-term follow-up.
3. Subjects must be 18 years of age or older at the date of consent.
4. Histologically confirmed diagnosis of secretory multiple myeloma (must have measurable M protein in serum or urine) with at least one of the following:
    - Serum M- protein ≥0.5 g/dL (≥5 g/L) for IgG, IgM, IgA or ≥0.05 g/dL for IgD; or
    - Urine M-protein ≥200 mg/24 hours; or
    - Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).
5. Subject must have documented diagnosis of relapsed and refractory multiple myeloma (RRMM) as described below:
    - subjects who have received at least 3 prior regimens and,

- were responsive to at least 1 or more prior regimens (as defined by IMWG criteria), and
- are refractory to their most recent therapy (≤ 25% response or progression during therapy or within 60 days after completion of therapy).

Prior therapies for subjects with RRMM must have contained at least one drug from each of the following drug classes: an immunomodulatory imide drug (IMiD), proteasome inhibitor, alkylator (unless the subject is ineligible or contraindicated to receive an alkylator), CD38 monoclonal antibody, and glucocorticoid as separate lines or a combined line of therapy. If prior therapy includes autologous stem cell transplantation (ASCT), then induction/ASCT/maintenance therapies will be considered as one line of therapy altogether.

Subjects who have relapsed after ASCT or are unable to receive ASCT are eligible. The interval from ASCT to entry in the study must be ≥12 weeks.

6. Left ventricular ejection fraction (LVEF) ≥50%. A lower LVEF (≥40%) is permissible if a formal cardiologic evaluation reveals no evidence for clinically significant functional impairment, otherwise the subject may not enter the study.
7. For subjects who have received prior checkpoint inhibitors or other immuno-oncology agents like T-cell receptor agonists:

    - Subjects with endocrine AE of any grade are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.
    - Must not have experienced any ≥Grade 3 AE nor any neurologic AE of any grade while receiving prior checkpoint inhibitors.
    - Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE related to checkpoint inhibitors, not have experienced recurrence of an AE related to checkpoint inhibitors if re challenged, and not currently require maintenance doses of corticosteroids.

    NOTE: see Exclusion Criterion 2 (prior PD-1/PD-L1 checkpoint blockade therapy for enrollment in Arm 2).

8. Subject has Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.

4.1.2. Leukapheresis (Part 2)

All screening criteria described in Section 4.1.1 must be reviewed and fulfilled along with all the following criteria prior to leukapheresis. Leukapheresis process may not be necessary for subjects for which NY-ESO-1c259T-cell product is already manufactured.

9. Subject is HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive as determined by a central laboratory. (This determination will be made under a pre enrollment screening ICF.

There are no restrictions on the timing of HLA typing for screening and data can be taken from subjects' records [see Section 3.2.1]).

10. Subject has confirmed sufficient expression of NY-ESO-1 and/or LAGE-1a by reverse transcription polymerase chain reaction (RT-PCR) as determined by a central laboratory contracted by the Sponsor (This determination will be made under a pre-enrollment screening ICF).
11. Subject has voluntarily agreed to participate by giving written informed consent for treatment in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and applicable local regulations.
12. In the Investigator's opinion, the subject is fit for cell collection.
13. The subject has the following laboratory parameters determined prior to leukapheresis according to timelines in the Apheresis Manual and which meet the requirements in the table below:

Absolute neutrophil count (ANC)	≥1.0 x 10^9/L
CD3 count	≥200/µL
Lymphocyte count	≥0.5 x 10^9/L

4.1.3. Lymphodepletion/treatment (Part 3)

All prior inclusion criteria described in Section 4.1.1 and Section 4.1.2 must be reviewed and fulfilled along with all the following criteria prior to lymphodepletion.

14. Subject has adequate vital organ function as indicated by the following laboratory values in the table below. Specimens must be collected no more than 7 days prior to start of lymphodepletion.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.0 × 10^9/L (without G-CSF support)
Platelets[a]	≥50 × 10^9/L
Hemoglobin	>80 g/L (8 g/dL) (without transfusion support within 7 days from start of leukapheresis)
Coagulation	
Prothrombin time (PT)[b] or International normalized ratio (INR)	≤1.5 × upper limit of normal (ULN)
Partial thromboplastin time (PTT)[b]	≤1.5 × ULN
Renal	

System	Laboratory Value
Measured or calculated[c] creatinine clearance	≥30 mL/min and not on dialysis
Hepatic	
Serum total bilirubin	≤1.5 × ULN (unless subject has documented Gilbert's Syndrome with direct bilirubin <35% of total bilirubin)
Aspartate aminotransferase (AST)/ Serum Glutamic Oxaloacetic Transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	≤2.5 × ULN

[a] Subjects should not have received platelet transfusion within 2 weeks of screening blood count.
[b] Unless receiving therapeutic anticoagulation, in which case PT or PTT should be within therapeutic range of intended use of anticoagulants.
[c] Subjects who are >18 or <65 years of age can be assessed using estimated creatinine clearance calculated using the Chronic kidney disease Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009]:
GFR = 141 x min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 *[if female]* × 1.159 *[if black] where*, Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min (Scr /κ, 1) indicates the minimum of Scr /κ or 1, and max (Scr /κ, 1) indicates the maximum of Scr /κ or 1.

Subjects ≥65 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.

15. Subject previously treated with BCMA therapy (BCMA CAR-T, ADC, or other type of BCMA-targeted therapy) must have progressed from this therapy prior to attending the Baseline visit prior to beginning lymphodepletion.
16. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    - Male subjects:

    Male subjects are eligible to participate if they agree to the following during the period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer.

- Refrain from donating sperm

Plus either:

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

OR

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

- Female subjects:

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

- Is not a WOCBP as defined in Section 6.3.3

OR

- Is a WOCBP (as defined in Section 6.3.3) 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 6.3.3 during the period starting at the Baseline Visit , for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer. If assigned to Arm 2 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 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.

- 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 subject must be excluded from participation if the serum pregnancy result is positive.

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

4.2. Subject Exclusion Criteria

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

4.2.1. Screening (Part 1)

1. Subjects with only plasmacytomas, plasma cell leukemia, monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), non-secretory myeloma or primarily amyloidosis.
2. Subject has already received one of the following therapy/treatment: anti-PD-1, anti-PD-L1, or anti-PD-L2 inhibitor. Note: this exclusion only applies to subjects who would be assigned to Arm 2.
3. Subjects who have previously participated in Merck pivotal trial NCT02576977: Study of Pomalidomide and Low Dose Dexamethasone With or Without Pembrolizumab (MK-3475) in Refractory or Relapsed and Refractory Multiple Myeloma (RRMM) (MK-3475-183/KEYNOTE-183).
4. Subject has received a prior allogeneic stem cell transplant.
5. Subject has toxicity from previous anticancer therapy that has not recovered to ≤ Grade 1 or to their baseline level of organ function (as outlined in inclusion criteria 14) prior to enrollment (except for non-clinically significant toxicities, e.g., alopecia, vitiligo). Subjects with Grade 2 toxicities that are deemed stable or irreversible (e.g. peripheral neuropathy) can be enrolled on a case-by-case basis with prior consultation and agreement with the Sponsor Study Physician.
6. Subject had major surgery within 4 weeks prior to enrollment (kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities.

7. Subject has history of allergic reactions to fludarabine, cyclophosphamide, or agents similar in chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study.
8. Known history of myelodysplasia.
9. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator assessment).

   NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice or cirrhosis.
10. Known history of chronic active hepatitis or liver cirrhosis (if suspected by laboratory studies, should be confirmed by liver biopsy).
11. Subject has an active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human T-lymphotropic virus (HTLV) as defined below:
    - Positive serology for HIV.
    - Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of chemotherapy.
    - Active hepatitis C subjects as demonstrated by test for hepatitis C ribonucleic acid (RNA). Subjects who are HCV antibody positive will be screened for HCV RNA by any RT-PCR or by DNA assay. If HCV antibody is positive, eligibility will be determined based on a negative screening RNA value.
    - Positive serology for HTLV 1 or 2.

    Re-screening for infection disease markers is not required at Baseline (prior to lymphodepleting chemotherapy).
12. History of severe immune disease, including non-infectious pneumonitis, requiring steroids or other immunosuppressive treatments.
13. Active immune-mediated diseases including:
    a. Connective tissue diseases, uveitis, sarcoidosis, inflammatory bowel disease, multiple sclerosis, (non-infectious) pneumonitis.
    b. Prior or active demyelinating disease
14. Evidence or history of significant cardiac disease (such as, but not limited to, unstable angina pectoris, myocardial infarction within the prior 6 months, heart failure within 6 months, symptomatic congestive heart failure, symptomatic or uncontrolled arrhythmias, severe aortic stenosis, symptomatic mitral stenosis).
15. QTc > 450 msec or QTc > 480 msec for patients with bundle branch block.

NOTES:

- The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
- The specific formula that will be used to determine eligibility and discontinuation for an individual subject 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 subject and then the lowest QTc value used to include or discontinue the subject from the trial.
- For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

16. Evidence or history of other significant hepatic, renal, ophthalmologic, psychiatric, or GI disease which would likely increase the risks of participating in the study.
17. Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers, carcinoma in situ of the breast, treated superficial bladder cancer or prostate cancer, or in situ cervical cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period. Long-term adjuvant therapy (example: breast cancer) is acceptable.
18. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
19. Active bacterial or systemic viral or fungal infections.
20. Pregnant or breastfeeding.

4.2.2. Leukapheresis/Manufacturing (Part 2)

A subject is not eligible for leukapheresis if any of the screening exclusion criteria described in Section 4.2.1 and any of the following criteria apply:

21. The subject has received or plans to receive the following treatment regimens and does not or cannot meet specified time frames prior to leukapheresis or lymphodepleting chemotherapy:

Treatment/Therapy	Required Wash-out
Cytotoxic chemotherapy	2 weeks
Immune therapy (including monoclonal antibody therapy)	No wash-out
Immunomodulator imide therapy (IMiD e.g. lenalidomide or pomalidomide)	No wash-out
Proteasome inhibitor therapy (e.g. bortezomib or carfilzomib)	2 weeks
Anticancer Vaccine	4 weeks The subject should be excluded if the Investigator considers their disease is responding to an experimental vaccine given within 6 months
Live-virus vaccination. NOTE: Seasonal flu vaccines that do not contain live virus are not an exclusion.	4 weeks
Allogeneic hematopoietic stem cell transplant at any time	Not permitted
Corticosteroids or any other immunosuppressive therapy. Note: Use of inhaled or topical corticosteroids, or of physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency is permitted.	2 weeks
Genetically engineered cell therapy	12 weeks
Investigational treatment (other than genetically engineered cell therapies)	4 weeks or 5 half-lives, whichever is longer
Radiotherapy	2 weeks
NOTE: Duration of any other anticancer therapies must be discussed with the Sponsor Study Physician	

4.2.3. Lymphodepletion/Treatment (Part 3)

A subject is not eligible for lymphodepletion if any of the screening or leukapheresis exclusion criteria described in Section 4.2.1 and 4.2.2, and any of the following criteria apply:

22. More than two years have passed since the last leukapheresis collection.

4.3. Completion of the Treatment Phase

A subject will be considered to have completed the treatment phase of the study when he/she has progression of disease or 108 weeks after NY-ESO-1^{c259}T-cell infusion, whichever is sooner (see Section 7.4.8 for disease response assessments) in order to allow for the primary analysis to occur.

All subjects completing the treatment phase will continue to be followed for observation of delayed AEs during the 15 years post-infusion in accordance with FDA [FDA, 2020] and EMA [EMA, 2009] regulations (see Section 7.4.9). While the follow-up including collection of delayed AEs (see Section 9.4) may start in this investigational protocol, subjects will ultimately be transferred to the LTFU protocol GSK208750 (ADP-0000-002) once meeting the conditions defined in Section 4.4. If the LTFU protocol is not available, subjects will be followed per the LTFU schedule of assessments detailed in Table 4 until the LTFU protocol becomes available. Once the LTFU protocol is available, if a subject declines to consent to the LTFU protocol, the subject will be considered completed in this study.

4.4. Conditions for Transfer to the LTFU Protocol – Study Completion

Subjects may be transferred to the LTFU as soon as their disease progression is confirmed and no later than 108 weeks after NY-ESO-1^{c259}T-cell infusion. If disease progression occurred prior to the Week 9 visit, subjects should remain on the treatment phase schedule to ensure collection of safety following T-cell infusion for a minimum of 9 weeks. If the LTFU protocol is not available, follow-up will start per guidelines detailed in Table 4 until the LTFU protocol becomes available.

Subjects who have been dosed with pembrolizumab will be followed for 24 months after their last dose of pembrolizumab, to ascertain if they are candidates to receive an allo-SCT transplant.

Subjects who received an allo-SCT within the 24-month follow-up period will be monitored for 18 months for post allo-SCT complications as defined in Section 9.5. This follow-up can be carried out under the current protocol or under the LTFU protocol.

This study will be considered complete when the last subject has been rolled over into the LTFU protocol.

4.5. Study Withdrawal

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or institution. However, the Investigator must make every reasonable effort to keep each subject on study for the whole duration of the trial. In cases where the subject is deemed ‘lost to follow-up’, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical records. Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with the primary reason as ‘Lost to Follow-up’.

If the subject withdraws consent for further participation in the study, all final End-of-Study assessments should be performed, if possible on the day the decision is made to take the subject off-study or as soon as possible thereafter. All of the results of the evaluations and observations, together with a description of the reasons for study withdrawal, must be recorded in the medical records and electronic Case Report Form (eCRF).

The following are some of the justifiable reasons for the Investigator to withdraw a subject from study:

- Withdrawal of consent.
- Did not receive any T cells (refer to Section 9.1 and Section 9.2 for continued monitoring of AEs/SAEs following study procedures).

If a subject who has consented to participate in pharmacogenetics research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options concerning the pharmacogenetics sample, if already collected:

- Pharmacogenetics research continues as per the subject's consent; *or*,
- Any remaining sample is destroyed

If a subject withdraws consent from the pharmacogenetics research or requests sample destruction, the Investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep study information collected/generated up and until that point.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in the Schedule of Assessments Table (see Section 8).

4.6. Discontinuation of Pembrolizumab Treatment (Arm 2 subjects)

A subject may discontinue pembrolizumab treatment prior to Week 108 per protocol-defined duration. The following are justifiable reasons for the Investigator to discontinue pembrolizumab permanently:

- disease progression
- toxicity criteria are met (according to Section 5.4.1) that require permanent discontinuation of pembrolizumab; *or*,
- subject's own decision due to unacceptable toxicities; *or*,
- subject who has attained negative minimal residual disease (MRD) status, who has been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

Once a subject discontinues pembrolizumab treatment, all assessments for the pembrolizumab treatment discontinuation visit should be performed, if possible on the day the decision is made to take the subject off-treatment or as soon as possible thereafter. Such subjects will be maintained in the interventional study until disease progression or 108 weeks after NY-ESO-

1^{c259}T-cell infusion, whichever is sooner, as for subjects in Arm 1, and will be following the same schedule for safety and disease assessment as Arm 1.

4.7. Considerations for Temporary Suspension of Enrollment

Throughout the conduct of the study, all safety data including SAEs and grade ≥3 AEs possibly associated with any of the 2 treatments (TCR or pembrolizumab) will be closely monitored and reviewed at each of the SRT meetings. The frequency of TLTs for Arm 2 subjects will also be assessed in a continuous manner (See Section 3.3). Based on the severity of the toxicities, indicators of potential antitumor activity, and other factors, a recommendation whether to suspend the treatment, or continue enrollment will be made with input from the SRT, Sponsor, and Investigators. Final decisions to halt or modify the study will be made by the Sponsor.

Furthermore, temporary suspension of enrollment or dosing will take place and regulatory authorities will be notified if any of the following events occur:

- Any event of Guillain-Barre syndrome (GBS) as diagnosed by a neurologist according to diagnostic guidance for GBS [Fokke, 2014] (refer to Section 10.3.1).
- A case of documented symptomatic progressive cerebral edema confirmed by an expert neurological examination and CT/MRI, that is not responding to treatment.
- Any death occurs that is deemed to be at least probably related to NY-ESO-1^{c259}T or the combination of NY-ESO-1^{c259}T and pembrolizumab; or
- Two (2) or more Grade 4 immune events are deemed at least probably related to NY-ESO-1^{c259}T or the combination of NY-ESO-1^{c259}T and pembrolizumab; *or*
- A subject has a positive test for replication competent lentivirus (RCL):
  - Confirmed positive PBMC RCL test and no other vector lot is available (refer to Section 10.1), *or*
  - Positive biological RCL test – all NY-ESO-1^{c259}T-cell infusions are halted (refer to Section 10.1).

Premature study termination may occur if:

- The Sponsor decides for any reason that subject safety may be compromised by continuing the study.
- The Sponsor decides to discontinue the development of the intervention to be used in this study.

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

4.8. Liver Chemistry Stopping Criteria

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

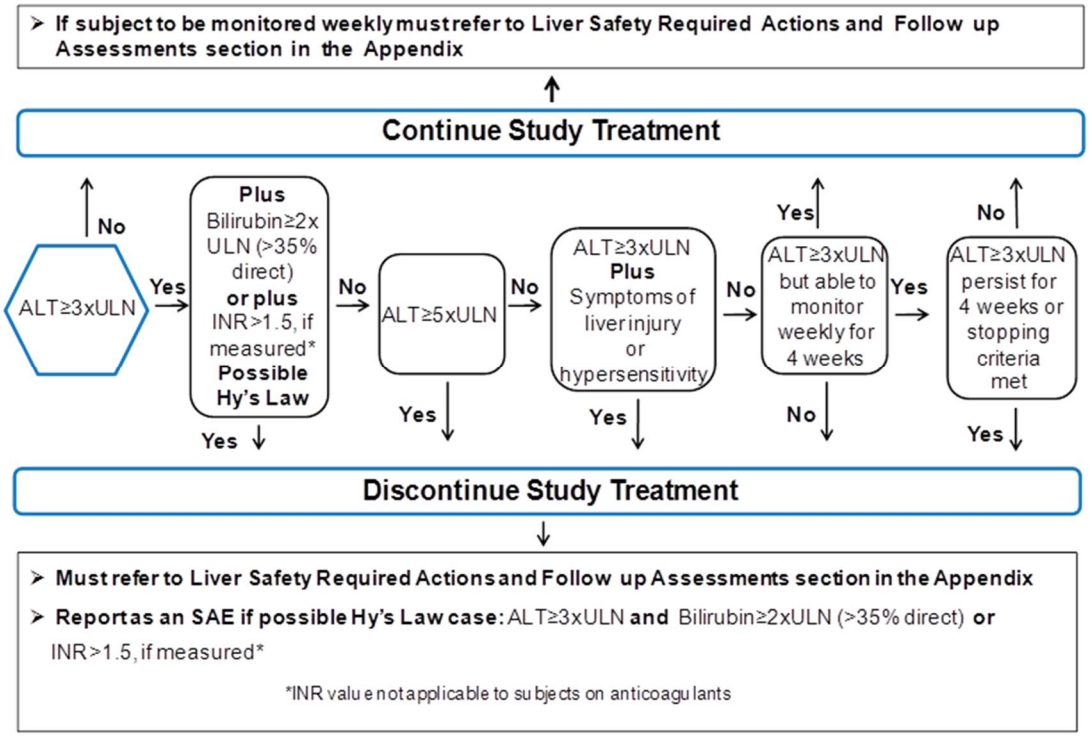
Discontinuation of study intervention for abnormal liver tests is required when:

- a subject meets one of the conditions outlined in the algorithm

  OR

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

Phase I/II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 16.6.

Study Intervention Restart after liver stopping criteria met

If subject meets liver chemistry stopping criteria do not restart subject 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 is signed by the subject

If GSK Medical Governance approval to restart subject with study treatment is not granted, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than drug-induced liver injury [DILI]) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Possible study DILI has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded.
- There is no evidence of alcoholic hepatitis.
- RC/IRB approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- Medical Monitor, and the RC/IRB as required, must be informed of the subject's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 8.10.

4.9. QTc Stopping Criteria

- QTc > 500 msec

  OR

- Change from baseline of QTc > 60 msec

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

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

5. STUDY TREATMENTS

5.1. Leukapheresis

Subjects who complete screening procedures defined in Section 7 and who meet all eligibility criteria defined in Section 4 will be eligible to undergo leukapheresis to obtain starting material for the manufacture of autologous NY-ESO-1^{c259}T.

For collection of starting material, a large-volume non-mobilized PBMC collection should be performed according to institutional standard procedures. The goal of the procedure is to collect a satisfactory cell count in the apheresis material prior to drug product manufacture. The target CD3+ cell count for drug product manufacture is $2.4x10^9$ CD3+ cells.

In cases where the minimum number of CD3+ is not collected or the T cells are not able to be infused back to the subject, a second apheresis may be performed. Additional aphereses may be performed in a case by case basis evaluation between the investigator and the Sponsor. Citrate anticoagulant should be used. Prophylaxis and treatment of adverse effects of the citrate anticoagulant (e.g. Ca gluconate, $CaCl_2$ or $MgSO_4$ infusions) may be administered at the discretion of the Investigator. The collected apheresis product will then be transported for manufacture as detailed in the Study Procedures Manual (SPM).

Once NY-ESO-1^{c259}T product has been manufactured, eligible subjects will proceed to have lymphodepleting chemotherapy and infusion of the study therapy as detailed in Section 5.2 and Section 5.3.

5.2. Lymphodepleting Chemotherapy

Prior to the administration of lymphodepleting chemotherapy baseline eligibility criteria will be re-confirmed and baseline tumor assessment obtained.

When the manufactured NY-ESO-1^{c259}T product has been received, the integrity of the bag(s) has been checked by the site, and the subject has been assigned to Arm 1 or Arm 2, fludarabine and cyclophosphamide will be used as lymphodepleting chemotherapy prior to administration of the study treatment as described in Table 1. For subjects with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia), the investigator should discuss with the sponsor's medical monitor or designee to determine the need for dose modification of the lymphodepletion regimen.

Appropriate IV hydration should be administered and Mesna given to prevent neurotoxicity while cyclophosphamide is administered, as described below. Other premedication (e.g., antiemetics) may also be provided in accordance with institutional standards. Steroids may be used as antiemetics for cyclophosphamide but must be discontinued no later than Day -3. G-CSF will be given to all subjects from 24 hours after the last dose of cyclophosphamide until resolution of neutropenia in accordance with American Society of Clinical Oncology (ASCO) guidelines or institutional practice (see Section 8.8.1).

On admission for lymphodepleting chemotherapy, subjects will commence antimicrobial and antifungal prophylaxis in line with institutional standard practice (see Section 8.2).

Table 1 Lymphodepleting Chemotherapy

Treatment schedule					**Recommended Prophylaxis and Supportive Medication**
Day[a]	**Drug**	**Dose**	**Route**	**Administration**	**Infection**: on admission for lymphodepleting chemotherapy, commence antimicrobial and antifungal prophylaxis (see Section 8.2), or in line with institutional guidelines. **Hydration:** Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions **Mesna:** may be given per institutional guidelines or as recommended in Section 5.2.3. **G-CSF:** start 24 hours post final cyclophosphamide until resolution of neutropenia[e] **Cell therapy premedication[f]:** the premedication with acetaminophen and diphenhydramine should be given approximately 30 minutes prior to the
-8	Fludarabine[b, c]	30 mg/m^2	IV	in 50-100 mL (concentration ≤1 mg/mL) of 0.9% NaCl over 30 min[g]	
-7	Fludarabine[b]	30 mg/m^2	IV	in 50-100 mL (concentration ≤1 mg/mL) of 0.9% NaCl over 30 min[g]	
	Cyclophosphamide[c]	900 mg/m^2	IV	in 100-250 mL 0.9% NaCl over 1 hour[g]	
-6	Fludarabine[b]	30 mg/m^2	IV	in 50-100 mL (concentration ≤1 mg/mL) of 0.9% NaCl over 30 min[g]	
	Cyclophosphamide[c]	900 mg/m^2	IV	in 100-250 mL 0.9% NaCl over 1 hour[g]	
-5	Fludarabine[b]	30 mg/m^2	IV	in 50-100 mL (concentration ≤1 mg/mL) of 0.9% NaCl over 30 min[g]	
	Cyclophosphamide[c]	900 mg/m^2	IV	in 100-250 mL 0.9% NaCl over 1 hour[g]	
-4	start **G-CSF**				
-3					
-2					
-1					
1	**NY-ESO-1^{c259}T infusion[d]**				

Treatment schedule		Recommended Prophylaxis and Supportive Medication
		NY-ESO-1^{c259}T infusion according to institutional practice

IV = intravenous; G-CSF= Granulocyte-colony stimulating factor

Notes:

[a] There is no Day 0 in this study.

[b] Fludarabine dose will be adjusted in renal impairment (see Section 5.2.2).

[c] For subjects ≥ 60 years of age, 3 doses of fludarabine (30 mg/m^2 on Days -7 to -5) and 600 mg/m^2 cyclophosphamide dose will be administered after consulting with the sponsor.

[d] Administration of NY-ESO-1^{c259}T is described in Section 5.3.

[e] Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. If pegylated G-CSF is administered, give one dose 24 hours after the last chemotherapy administered.

[f] Doses of supportive medications per institutional practice.

[g] Or per institutional standards.

5.2.1. Lymphodepletion Dose Modification

For participants ≥ 60 years old, the recommended lymphodepleting regimen will be as follows:

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

In case of participants with documented history of severe and prolonged cytopenia (anemia, thrombocytopenia, or leukopenia), the investigator should discuss with the sponsor's medical monitor or designee the opportunity for potential lymphodepletion dose adjustment

5.2.2. Fludarabine Dose Adjustment for Renal Impairment

The dose of fludarabine will be adjusted for subjects with renal dysfunction as follows:

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

5.2.3. Mesna

Mesna will be given to cover the duration of cyclophosphamide chemotherapy according to institutional practice or the following recommendation:

20% cyclophosphamide dose (i.e., 180 mg/m^2) as an IV bolus pre-infusion and 3 h, 6 h, and 9 h on each day of cyclophosphamide administration.

5.3. T-cell Infusion

The autologous T cell transduced with lentivirus encoding enhanced TCR specific for NY-ESO-1^{c259} is one of the IPs in this study.

Subjects will receive transduced T cells in the range of 1×10^9 to 8×10^9 cells. If the transduced cell dose is less than the minimum dose of 1×10^9, manufacturing of additional transduced T-cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the range 1×10^9 to 8×10^9. In the event that no banked leukapheresis product is available a second leukapheresis may be performed. The cells will be pooled and administered by a single IV infusion on Day 1.

5.3.1. Premedication

Premedication with antihistamine and acetaminophen can help prevent infusion reactions and should be administered prior to the T-cell infusion as per institutional standards. Steroids should not be administered because they are cytotoxic and inhibitory to the T-cell product.

5.3.2. Cell Infusion

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

On Day 1, the participant will receive thawed GSK3377794 by IV infusion. Prior to infusion, two clinical personnel will independently verify and confirm in the presence of the subject that the information on the infusion bag is correctly matched to the subject, as per the Sponsor's and clinical site's procedures.

The specific instructions for the preparation and administration of GSK3377794 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 adverse reaction to the cell infusion, the infusion rate should be reduced and the reaction managed according to institutional standard procedures. Steroid treatment should be avoided unless medically required. In the event a subject develops a febrile episode following the infusion, appropriate cultures and medical management should be initiated, with attention to the initiation of empirical antibiotic treatment in the case of febrile neutropenia (see Section 8).

The day of T-cell infusion may be delayed in subjects with significant complications of chemotherapy if, according to the Investigator, it is in the best interest of the subject. The timing of all assessments and procedures post-infusion will be calculated with reference to the T-cell infusion date (Day 1). Eligible subjects who do not receive the NY-ESO-1^{c259}T infusion for any reason may be replaced. Cytopenias alone should not be a reason to delay T-cell infusion unless complications are present.

Vital signs will be recorded prior to the infusion; and 5, 15, 30 minutes, 1, 1.5, 2 and 4 hours after the infusion has started.

5.4. Pembrolizumab (Arm 2) Infusion

Pembrolizumab will be administered on Day 22, 21 days after the T-cell infusion (the day when NY-ESO-1^{c259}T is infused, is considered Day 1, there is no Day 0 in this study), and every 3 weeks thereafter up to Week 108. If subject is experiencing toxicities preventing dosing of

pembrolizumab at Week 3, the first dose of pembrolizumab may be administered on Week 6 instead. If subject is still experiencing toxicities preventing starting pembrolizumab dosing at Week 6, this subject will not be administered pembrolizumab and will be followed for visits as a subject in Arm 1.

Pembrolizumab will be administered as a fixed 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 minutes -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

When pembrolizumab is administered with NY-ESO-1^{c259}T, it is expected that the checkpoint blockade will activate the immune system. This may lead to enhanced antitumor activity as well as toxicity (refer to Section 3.1.2).

5.4.1. Schedule Modification Guidelines for Pembrolizumab (Arm 2)

AEs (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Table 2 below lists severe or life-threatening AEs and conditions where pembrolizumab treatment must not be started or must be withheld for drug-related toxicities. If pembrolizumab cannot be started at Week 3 due to an AE, subjects in Arm 2 may receive their first dose of pembrolizumab on Week 6. See Section 8.9 for supportive care guidelines for management of pembrolizumab toxicities.

In special situations not specified below, Sponsor must be contacted.

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, subject vacation, and/or holidays). Subjects 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 subject's study record.

Table 2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:
Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects 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 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus).

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	Grade 4	Permanently discontinue		Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Subjects 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 substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
[1]Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. NOTE: For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

6. CONCOMITANT MEDICATION AND TREATMENT

6.1. Prohibited Concomitant Medication and Treatment

Subjects are prohibited from receiving the following therapies during the screening and treatment phases of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the Sponsor. Subjects receiving any of palliative radiation therapy that could be foreseen impacting disease course or disease assessments will be censored for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist™) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to treat an event of suspected immunologic etiology (see Section 8). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. According to local standard of care or ASCO guidelines [Basch, 2011], steroids may be used as antiemetics with cyclophosphamide but must be discontinued no later than 3 days prior to infusion of NY-ESO-1^{c259}T. Topical steroids for cutaneous application, orally non-absorbable and inhaled steroidal treatments are permitted.
- Herbal remedies.

Subjects who undergo any active anticancer therapy other than the protocol-defined IP(s) will be considered as having met the progressive disease (PD) criterion for efficacy and will be rolled over to the LTFU protocol GSK208750 (ADP-0000-002).

Subjects may receive other medications that the Investigator deems to be medically necessary.

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

There are no prohibited therapies during the LTFU phase.

6.2. Permitted Concomitant Medication and Treatment

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

Other treatment that the Investigator considers necessary for a subject's welfare may be administered during the treatment 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 subject at high risk for vaccine-preventable disease (or member of the subject's household), consult an Infectious Disease specialist or a guidance such as the CDC Clinical Practice Guideline for Vaccination of the Immunocompromised Host.

All concomitant medications will be recorded, including all prescription and over-the-counter (OTC) medications and herbal remedies including dose and frequency. Any changes to concomitant medication regimens should be recorded throughout the study in the eCRF.

6.3. Restrictions

6.3.1. Corticosteroids

Corticosteroids may diminish the antitumor activity effects of the NY-ESO-1-^{c259}T product. Consider alternatives to steroid therapy when possible. However, for symptom management as indicated in Section 8 or in case of any life-threatening conditions, steroids should not be withheld.

6.3.2. Diet

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

6.3.3. Contraception

Both IPs, NY-ESO-1^{c259}T and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if NY-ESO-1^{c259}T and pembrolizumab have transient adverse effects on the composition of sperm.

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Woman in the following categories are not considered WOCBP

1. Premenarchal

Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

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

Postmenopausal female

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

Contraception

Male subjects:

Male subjects must agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer.

- Refrain from donating sperm

Plus either:

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

OR

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

Female subjects:

WOCBP must agree to the following during the intervention period starting at the Baseline Visit for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/ gene modified cells in the subject's blood, whichever is longer. If assigned to Arm 2, 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 and gene modified cells.

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

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device
Intrauterine hormone-releasing system
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]

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] oral injectable
Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subjectt*
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. If locally required, in accordance with Clinical Trial Facilitation Group 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 are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the Baseline Visit throughout the study period up to 12 months after receiving T-cell infusion, or up to 4 months after there is no evidence of persistence/gene modified cells in the subjects' blood, whichever is longer. Subjects in Arm 2 must also use effective contraception for at least 4 months after the last dose of pembrolizumab. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.3.4. Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject'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 Study 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.

6.3.5. Use in Nursing Women

It is unknown whether 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, subjects who are breastfeeding are not eligible for enrollment.

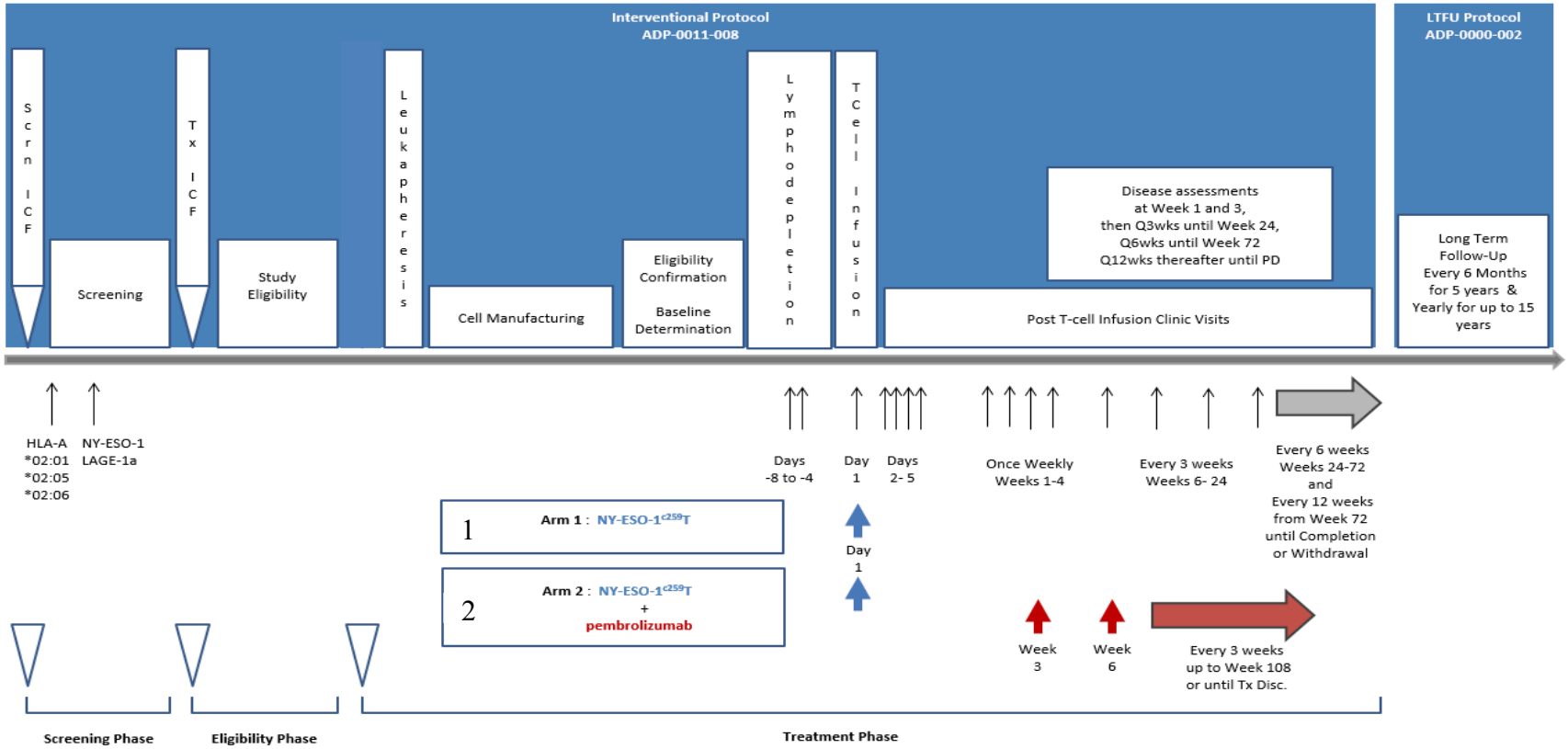
7. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The Schedule of Procedures for this study is provided in Table 3.

Subjects will be assigned a unique subject number upon signing the Screening ICF. Upon qualification based on HLA and antigen profile (Section 7.1), subjects will be asked to sign the Treatment ICF to be further assessed for eligibility. The number assigned at screening will serve as the subject ID as well as for the enrollment, post-qualification, into the treatment phase of this study. Study procedures performed as part of standard of care prior to signing informed consent can be used for screening if they were performed within 7 days prior to leukapheresis for laboratory tests, pregnancy , and infectious disease screen, and within 4 weeks prior to leukapheresis for ECHO/MUGA, brain MRI, and ECG (including cardiac stress test) (see Section 7.3). Please follow guidance in Apheresis Manual for timing of lab tests for CD3 counts, ANC, and lymphocyte counts prior to leukapheresis.

Figure 2 presents the overall patient journey from pre-enrollment screening through study completion or withdrawal.

Figure 2 Schematic for Study GSK208470 (ADP-0011-008)



Between leukapheresis and lymphodepletion, in the place of bridging therapy, an experimental line of therapy can be given (such as a BCMA-targeted agent) under another study protocol, including with another Sponsor.

Subjects receiving an experimental line of therapy between leukapheresis and lymphodepletion must have progressive disease from this intermediate line of therapy before receiving lymphodepletion in this study.

7.1. HLA and Antigen Screening

Subjects who are identified by the Investigator as possible candidates for the trial must be tested for their HLA-genotype and for expression of NY-ESO-1 and/or LAGE-1a antigens. The HLA and antigen screening tests must be positive prior to conducting the remaining study screening procedures for eligibility.

7.1.1. Blood sample for HLA subtyping

HLA-genotyping at the allelic level (4-digit) will be carried out on a blood sample by a central laboratory using a high-resolution Sequence-Based Typing assay.

7.1.2. Bone marrow aspirate for antigen testing by RT-PCR

Determination of NY-ESO-1 and/or LAGE-1a expression will be carried out using quantitative reverse transcription-polymerase chain reaction (PCR) on RNA isolated from fresh bone marrow aspirate samples obtained in accordance with routine clinical practice.

The requirements for the aspiration procedure, processing of the bone marrow aspirate sample, as well as quantity and quality are outlined fully within the SPM. Briefly, to ensure the highest quality of the sample, and to ensure sufficient quantity for multiple biomarker analyses, bone marrow samples must be collected in PAXgene tubes, processed and submitted directly to the reference laboratory for analysis of antigen expression as outlined within the SPM.

Additional assay platforms which may be utilized include but are not limited to: Ribonucleic Acid Sequencing (RNA-Sequencing) and RNA expression analysis.

In the event that the bone marrow sample submitted for diagnostic analysis is of insufficient quantity or quality (e.g. low plasma cell content) to conduct the testing and determine the subject's antigen expression profile, additional bone marrow sample(s), obtained in accordance with routine clinical practice, may be submitted to the central laboratory.

7.1.3. Bone Marrow Sample Banking and Storage

Following diagnostic analysis of a subject's bone marrow specimen at the central reference laboratory, remaining sample (residual RNA) will be banked and stored at a GSK-specified biorepository for the validation of single- and/or multiple-biomarker companion diagnostic assay(s) (Refer to Section 7.1.4). The central reference laboratory will forward the remaining samples directly to the biorepository. The central reference laboratory will enclose a copy of the pathology report or the pathological description of the specimen with each sample along with a Sample Transmittal Form. Residual bone marrow RNA samples will be assigned a unique tracking number, will be logged into the biorepository's Laboratory Information Management System, and will be stored at -80°C. Samples will be retained for up to 15 years after the study is closed, after which time the samples will be either returned to the site or disposed of.

7.1.4. Companion Diagnostic Development

Following screening for the antigen expression, remaining screening sample may be used for the purpose of developing and validating single- and/or multiple-marker IVD assays for antigen screening for regulatory approval of a therapeutic new product indication. Bone marrow samples may be used for the analytical validation (which includes testing for efficiency, sensitivity, specificity, exclusivity, accuracy and precision), as well as the clinical validation of such diagnostic assays. Validated and regulatory approved companion diagnostic assays may be used in the future to precisely determine subjects' antigen expression profile so as to determine the most appropriate targeted T-cell therapy treatment.

7.2. Screen Failures

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

Screen Failure data including demographics, SAEs, and reason for failing screening will be collected in the eCRF.

7.3. Schedule of Procedures

Table 3 Schedule of Procedures

	Screening[a] Phase / Eligibility Phase			Treatment Phase																		DC of Pembrolizumab Tx[c]	Completion of Treatment Phase or WD[d]
			Leukapheresis	Baseline ≤7 days prior to chemo	Lymphodepleting Chemotherapy[b]					T-cell infusion													
Study Day	**Scrn**	**Elig**		**D -14 to D -8**	**D -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D 1**	**D2**	**D3**	**D4**	**D5**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk 15**	**Wk 24 & Q12wks**		
Window															**±1D**	**±1D**	**±1D**	**±3D**	**±3D**	**±3D**	**±7D**		
Informed consent[a]	X	X																					
Demographics	X																						
HLA-genotyping	X																						
NY-ESO-1 and LAGE-1a levels on BM aspirate	X																						
Inclusions/ Exclusions		X		X																			
Baseline characteristics[e]				X																			
Medical History[f]		X																					
Physical Exam[g]		X		X																	X		
Prior/Concomitant medication[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS		X		X						X					X	X	X	X	X	X	X	X	X
Vital signs / Weight		X		X						X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry		X		X																			
ECG		X[j]		X[j]						X			X		X								
Echo / MUGA		X[a,k]																					
Brain MRI[l]		X								See footnote 'l'													
ICE[m]										See footnote 'm'													
Chest X-ray (if indicated)		X																					
Hematology		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation tests[n]		X		X																			

	Screening[a] Phase / Eligibility Phase			Treatment Phase																		DC of Pembrolizumab Tx[c]	Completion of Treatment Phase or WD[d]
			Leukapheresis	Baseline ≤7 days prior to chemo	Lymphodepleting Chemotherapy[b]					T-cell infusion													
Study Day	**Scrn**	**Elig**		**D -14 to D -8**	**D -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D 1**	**D2**	**D3**	**D4**	**D5**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk 15**	**Wk 24 & Q12wks**		
Window															**±1D**	**±1D**	**±1D**	**±3D**	**±3D**	**±3D**	**±7D**		
Pregnancy test[o]		X		X	X					X							X		X	X	X	X	X
Urinalysis[n]		X		X																			
Infectious Disease screen[p]	X	X		X																			
CMV PCR[q]		X		X						X					X			X	X				
Thyroid Function Tests[n]				X						X									X then Q6wks (Arm 2 only) →				
C-Reactive Protein[r]				X						X				X			X		X				
Uric acid				X						X													
GFR or 24h urine creatinine[s]		X		X																			
Adverse Events[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vector Copies (Persistence for safety)[u]										X										X	X[u]		
VSV-G DNA (RCL) for safety[u]										X										X	X[u]		
Leukapheresis, Lymphodepleting Chemotherapy																							
Leukapheresis[v]			X																				
Fludarabine					X	X	X	X															
Cyclophosphamide						X	X	X															
G-CSF[w]									X														
Administration of Investigational Products																							
NY-ESO-1^{c259}T infusion										X													
Pembrolizumab (Arm 2 only)[x]																	X then Q3wks up to Wk108 →						

	Screening[a] Phase / Eligibility Phase			Treatment Phase																		DC of Pembrolizumab Tx[c]	Completion of Treatment Phase or WD[d]
			Leukapheresis	Baseline ≤7 days prior to chemo	Lymphodepleting Chemotherapy[b]					T-cell infusion													
Study Day	**Screen**	**Elig**		**D -14 to D -8**	**D -8**	**D -7**	**D -6**	**D -5**	**D -4**	**D 1**	**D2**	**D3**	**D4**	**D5**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk 15**	**Wk 24 & Q12wks**		
Window															**±1D**	**±1D**	**±1D**	**±3D**	**±3D**	**±3D**	**±7D**		
Multiple Myeloma Disease Assessments																							
Myeloma markers (labs)[y]		X		X											X		X then Q3wks until Wk24, Q6wks until Wk72, Q12wks thereafter until confirmed PD →					X	X
Bone marrow sample[aa, ab]		X[z]		X													X			X	X		X
Bone imaging[ac]				X																X	X		
Research Assessments																							
Pharmaco-genetic - Whole Blood Sample				X[ad]																			
Bone marrow (bone marrow mononuclear cells)[ae]				X															X	X	X		X
Cell pheno-typing & Functional assays - PBMC				X										X	X	X	X	X	X	X	X	X	X
Vector Copies (Persistence for Research)				X						X				X	X	X	X	X	X				X
Cytokine analyses & Anti-TCR antibodies[r]				X						X[r]		X		X	X	X	X	X	X[r]	X	X[r]	X	X
Soluble BCMA (sBCMA)				X						X		X		X	X	X	X	X	X	X	X	X	X
cfDNA and exosomes		X		X															X	X	X		X

BM = bone marrow; CBC = complete blood count; CMV = cytomegalovirus; CRP = C-reactive protein; DC = discontinuation; DNA = deoxyribonucleic acid; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; Elig = Eligibility; G-CSF = granulocyte-colony stimulating factor; HBV = hepatitis

B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; HTLV = human T-lymphotropic virus; IMWG = International Myeloma Working Group; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scan; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PS = Performance Status; RCL = replication competent lentivirus; Scrn = Screening; Tx = treatment; VSV-G = vesicular stomatitis virus envelope glycoprotein; WD = study withdrawal

a. Written subject informed consent (and subject assent as applicable) must be obtained prior to performing any protocol procedures. An initial Screening informed consent must be signed prior to obtaining a blood sample for HLA-testing and bone marrow aspirate for antigen testing. The Treatment informed consent must be signed prior to all other screening procedures. ECHO/MUGA scans, brain MRI, and ECG (including cardiac stress test) must be completed within 4 weeks prior to leukapheresis. Hematology, chemistry, coagulation tests, urinalysis, GFR or 24-hour urine creatinine as appropriate, and the infectious disease panel [HIV, HBV, HCV, HTLV, EBV, CMV, and syphilis (spirochete bacterium)] must be completed no more than 7 days prior to leukapheresis. Absolute neutrophil count, absolute lymphocyte count, and CD3+ count must be completed prior to leukapheresis according to timelines in the Apheresis Manual. Laboratory tests performed as standard of care and within the specified time frames will be accepted.

b. Lymphodepleting chemotherapy may only be initiated after the manufactured NY-ESO-1^{c259}T-cell product has been received at the site and the bag(s) have passed inspection by site personnel (see further details in study procedures manual [SPM]).

c. Only for subjects enrolled on Arm 2: if subject discontinues from pembrolizumab treatment prior to relapse/progression, this treatment discontinuation visit must be performed including all indicated procedures and assessments listed, unless already recently performed within 30 days. Subject will be maintained in the interventional protocol until disease progression or 108 weeks after NY-ESO-1^{c259}T-cell infusion, whichever is sooner, following the same schedule for safety and disease assessment as Arm 1, and will be transferred to the LTFU protocol GSK208750 (ADP-0000-002) as soon as they meet conditions defined under Section 4.4. If the LTFU protocol is not available, follow-up will start per guidelines detailed in Table 4 until the LTFU protocol becomes available.

d. If subject withdraws from the treatment phase prior to disease progression, a completion/withdrawal visit must be performed including all procedures and assessments listed indicated, unless already recently performed within 30 days. All subjects will be transferred to the LTFU protocol GSK208750 (ADP-0000-002) upon completion/withdrawal from treatment phase as soon as they meet conditions defined under Section 4.4. If the LTFU protocol is not available, follow-up will start per guidelines detailed in Table 4.

e. Baseline characteristics include recording time from initial diagnosis and time from last therapy.

f. Includes prior lines of therapy.

g. Physical examination will only be collected at screening and baseline and every 6 months – any abnormal findings outside these time points will be reported as an AE.

h. Includes concomitant medication since last visit.

i. Vital signs (temperature, pulse, respirations and blood pressure) on the day of T-cell infusion should be taken pre-infusion; and at 5, 15 and 30 minutes, and 1, 1.5, 2, and 4 hours after infusion has started.

j. Cardiac stress test is performed for subjects who are 55 years of age or over (specificity of the test will be at Investigator's discretion).

k. MUGA and/or ECHO are required at screening. May also be performed post-lymphodepleting chemotherapy if clinically indicated at the discretion of the Investigator. For subjects with cardiac or pericardial disease at baseline, inpatient telemetry monitoring will be carried out for a minimum of three and up to seven days post NY-ESO-1^{c259}T infusion.

l. Brain MRI (or CT Scan if MRI not feasible) should be obtained in all subjects at the time of screening within 4 weeks prior to leukapheresis. Baseline brain MRI should be repeated if more than 4 months have elapsed prior to lymphodepletion.

m. Immune Effector Cell-Associated Encephalopathy (ICE) should be measured on the day of NY-ESO-1^{c259}T-cell infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. Subjects with known brain metastases should be monitored at least twice per day for the first 5

days following NY-ESO-1^{c259}T-cell infusion. If a subject is found to have Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), the ICE neurological assessment tool should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

n. Additional tests may be performed at any time if clinically indicated.

o. Pregnancy test for women of childbearing potential (WOCBP) only. Urine or serum pregnancy test (highly sensitive) is to be performed and confirmed negative at screening, prior to lymphodepleting therapy, prior to NY-ESO-1^{c259}T-cell infusion, prior to each dose of pembrolizumab, at discontinuation of pembrolizumab, and at the completion/withdrawal visit.

p. Testing for infectious disease markers [HIV, HBV, HCV, HTLV, EBV, CMV, and syphilis (spirochete bacterium)] is required at screening, within 7 days prior to leukapheresis, and at Baseline. Subjects who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT-PCR or bDNA assay.

q. CMV seropositive subjects will continue to be monitored at least every 3 weeks for CMV viremia by CMV DNA PCR until 9 weeks post T-cell infusion (Section 8.2.3)

r. Sample for cytokine levels at Day 1 will be collected pre-infusion. If cytokine release syndrome (CRS) is suspected, cytokine levels as well C-reactive protein levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed. Anti-TCR antibodies will be assessed from the same collection as for cytokines but only at Baseline, Week 6 and Week 24.

s. Only for subjects ≥65 years of age.

t. Refer to Section 9.1 for instructions and details of AE collection and periods.

u. Vector Copies (Persistence) and VSV-G DNA (RCL) are Central Labs. Vector copies for safety samples are collected Day1 (pre-infusion) and at Week 15, Week 24, and Week 48 post T-cell infusion, then every 6 months post T-cell infusion from year 2-5, and annually from year 6-15. RCL samples are collected Day1 (pre-infusion), and at Week 15, Week 24, and Week 48 post T-cell infusion, and then annually.

v. Testing of subject leukapheresis will meet regional legislative requirements. In the EU this may include screening for Treponema pallidum (syphilis), details will be defined in the SPM.

w. G-CSF will be given from 24 hours after the last dose of cyclophosphamide until resolution of neutropenia in accordance with American Society of Clinical Oncology (ASCO) guidelines or institutional practice. Long-acting (pegylated) G-CSF may be substituted according to institutional practice as described in Section 8.8.1.

x. Subjects in Arm 2 will receive 200 mg pembrolizumab IV for the first time on Week 3. The second dose of pembrolizumab will be administered three (3) weeks later, at Week 6, and subsequent doses of pembrolizumab will be administered every 3 weeks thereafter up to Week 108 post T-cell infusion. If toxicities that preclude pembrolizumab treatment (such as CRS Grade ≥2) are observed at Day 22 (Week 3), infusion of pembrolizumab will start on Week 6. If toxicities have not resolved by Week 6, pembrolizumab will not be administered and the subject will be followed for visits as a subject in Arm 1. Schedule adjustments are outlined in the protocol (Section 5.4.1).

y. SPEP + immunofixation; quantitative IgG, IgM, IgA; UPEP + immunofixation based on 24-hour urine collection; serum free κ and λ light chain levels and κ/λ ratio determination; beta-2-microgobulin.

z. The BM sample is optional for eligibility if subject had prior histological confirmation of the disease.

aa. BM sampling should be preferably a fresh aspirate; aspirates are required at Screening, Baseline, Week 3 (before pembrolizumab infusion in Arm 2) as well as for MRD analysis.

ab. BM samples will be obtained at Baseline, at Week 15 and at Disease Progression (before starting a new treatment) per standard of care and at the time of a complete response assessment (per IMWG response criteria [Kumar, 2016]). If the subject received systemic anticancer therapy between leukapheresis and lymphodepleting chemotherapy for disease control, then the timing of the BM sample at baseline is critical and must respect the wash-out periods of Exclusion criterion # (Section 4.2). A BM sample will also be collected at Week 3 or at Week 6 if the scheduled Week 3 infusion of pembrolizumab is delayed to Week

6. Any BM sampling at Week 24 and subsequent Q12wks visits are up to PI's discretion if not required for response assessment per IMWG criteria [Kumar, 2016]. A BM sampling should also be analyzed at the time of a complete response (CR) assessment as per IMWG criteria [Kumar, 2016], in order to confirm CR. Additional BM samples for research purposes semi-annually (optional) or whenever follow-up marrow collection may be performed at PI's discretion. The BM sample obtained at the time point believed to be the closest to maximum response will be analyzed for Minimal Residual Disease (MRD). Refer to Section 7.5.3 for further specific details. **For subjects in Arm 2, the bone marrow aspirate must be taken prior to the pembrolizumab infusion on those visits at which both are scheduled.**

ac. Bone imaging (CT, MRI, PET, or bone survey) is required at baseline.. Additional imaging, only if clinically indicated, is scheduled at Week 15 and Week 24 then every 12 weeks.

ad. If pharmacogenetics sample collection is not done at baseline, it may be done at any other subsequent visit while the subject is in the treatment phase of the study. Collection of pharmacogenetics sample is optional and all subjects who participate must provide consent for pharmacogenetics blood sample collection.

ae. Will be conducted every time a BM sample is obtained. Research includes tumor antigen, gene marked T cells, T-cell clones and cytokines. Cytogenetics should be performed at least at baseline and at relapse.

Table 4 Schedule of Procedures in Long-Term Follow-up Phase Prior to Transfer to LTFU Protocol

Time post-infusion												
	Year 1			**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Years 6-15**
Months	3	6	12	18	24	30	36	42	48	54	60	Annually
Visit window	± 2 weeks		± 3 month									± 6 months
Safety Assessments												
Medical History and Physical Exam[1]	X	X	X	X	X	X	X	X	X	X	X	X
Mutagenic agents, other investigational agents or anti-cancer therapies[1]	X	X	X	X	X	X	X	X	X	X	X	X
Delayed adverse events and serious adverse events[2]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X		X		X		X		X	X[3]
Serum chemistry	X	X	X		X		X		X		X	X[3]
Pregnancy test (for WOCBP)[4]	<==========X[4]==========>											
Monitor for allo-SCT[5]	X	X	X	X	X	X	X	X	X			
Central Lab												
VSV-G DNA (RCL) for safety[6]	X	X	X		X		X		X		X	X
Vector copies (persistence) for safety[7]	X	X	X	X	X	X	X	X	X	X	X	X[3]
Other Assessments												
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X

1. New medical history/medications/chemotherapies.
2. Delayed adverse event collection is limited to:
   - New malignancies
   - New incidence or exacerbation of a pre-existing neurologic disorder
   - New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
   - New incidence of an immune-related hematologic disorder

- Serious infections (including opportunistic)
- Unanticipated illness and/or hospitalization deemed related to gene modified cell therapy
- Specific events outlined in Section 9.5 for subjects who received pembrolizumab and had allo-SCT

3. In year 6-15, laboratory assessments are performed for as long as persistence is analyzed. If persistence samples are discontinued (Section 10.1.3.1 and Section 10.1.3.2) then laboratory assessments are discontinued.
4. For WOCBP, pregnancy testing should be conducted during contraception period only as defined in Section 4.1, Inclusion Criteria. When pregnancy testing is performed at visits where hematology sample is collected, blood pregnancy testing will be done. At visits where hematology testing is not performed, urine pregnancy test is acceptable unless serum testing is required by local regulation or IRB/IEC.
5. All subjects who received pembrolizumab will be followed for a potential allo-SCT for 2 years following the last dose of pembrolizumab. Subjects who receive an allo-SCT within the 24-month follow-up period will be monitored for 18 months for post-allo-SCT complications as stated in Section 9.5.
6. Samples for RCL (VSV-G copies) are collected as described in Section 10.1.1.
7. Samples for persistence are collected as described in Section 10.1.3.1, and Section 10.1.3.2.

7.4. Clinical Assessments and Procedures

7.4.1. Medical History

A complete medical history (including demographics) will be recorded at screening in the subject's medical record and eCRF.

7.4.2. Physical Examination and Measurement of Vital Signs

At screening for eligibility and baseline, subjects will undergo a physical examination including weight, height (collected only once), and measurement of their vital signs (temperature, pulse, respirations, and blood pressure [BP]). The frequency of physical examination, weight and vital signs assessments at subsequent visits is specified in the Schedule of Procedures (Section 7.3).

7.4.3. Performance Status

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

7.4.4. Clinical Safety Assessments

Subjects will be assessed for AEs throughout the study. AEs are to be graded by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 unless specified otherwise in this protocol (see Table 5 in Section 8.5 for grading of CRS and Section 8.6.2 for grading of GVHD). All AEs must be recorded in the eCRF.

Details on assessing and reporting AEs and SAEs are described in Section 8.10.

7.4.5. Laboratory Assessments

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

Refer to Section 16.3 for listings of laboratory tests to monitor subject safety.

Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening, prior to starting lymphodepleting chemotherapy, prior to NY-ESO-1^{c259}T-cell infusion, prior to each dose of pembrolizumab, at discontinuation of pembrolizumab, and at the completion/withdrawal visit.

Please refer to Schedule of Procedures (Section 7.3) for additional information regarding the frequency of these assessments.

7.4.6. Cardiac Assessments

All cardiac assessments will be performed locally at the site.

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

- An ECHO or MUGA scan will be performed at screening to determine eligibility. Additional scans will be performed only if clinically indicated. NOTE: the same method of cardiac evaluation must be used consistently for any follow-up scans.
- ECGs refer to Section 16.3 for the ECG parameters required.

Please refer to Schedule of Procedures (Section 7.3) for information regarding the frequency of these assessments. For subjects with cardiac or pericardial disease at baseline, inpatient telemetry monitoring will be carried out for a minimum of three and up to seven days post NY-ESO-1^{c259}T infusion. Reports of cardiac events in subjects with cardiac or pericardial masses following treatment with NY-ESO-1^{c259}T will continue to be monitored through normal proactive pharmacovigilance.

7.4.7. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Please refer to Section 8.10 for information related to the grading and management of ICANS. Brain MRI (or CT Scan if MRI not feasible) should be obtained in all subjects at the time of screening. Baseline brain MRI should be repeated if more than 4 months have elapsed prior to lymphodepletion.

Immune Effector Cell-Associated Encephalopathy (ICE) should be measured on the day of NY-ESO-1^{c259}T infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. Subjects with known brain metastases should be monitored at least twice per day for the first 5 days following NY-ESO-1^{c259}T infusion. If a subject is found to have ICANS, the ICE tool should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

7.4.8. Disease Response Assessments

Assessments for response and progression will be evaluated at baseline and throughout the study (refer to the Schedule of Procedures; Section 7.3) according to the IMWG Uniform Response Criteria for Multiple Myeloma [Kumar, 2016].

Diagnosis criteria will be as described in the IMWG Criteria for the Diagnosis of Multiple Myeloma (see Section 16.4).

7.4.9. Long-Term Follow-up

All subjects will be followed for survival, and for 15 years from time of T-cell infusion for observation of delayed AEs in accordance with FDA and EMA requirements for gene therapy clinical trials [FDA; 2020; FDA, 2010; EMA, 2009]. These assessments may be collected in the Interventional Phase of the study and will be collected thereafter in the LTFU protocol (GSK208750 [ADP-0000-002]).

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

7.4.10. Allogeneic Stem Cell Transplantation and Follow-up

For subjects who received pembrolizumab and who have an allogeneic stem cell transplant (allo-SCT) within 24 months of last dose of pembrolizumab, transplant parameters will be collected, and specific and medically important adverse events post-allo-SCT will be collected for 18 months from the date of the allogeneic transplant (see Section 9.5). This follow-up can be carried out under the current protocol or under the LTFU protocol.

If available and relevant to an event post- allo-SCT, concomitant medications and/or laboratory results may also be reported.

7.5. Correlative Studies and Research Assessments

Correlative studies and research assays will be performed during the trial with the aim of monitoring the biological parameters that influence treatment outcome, such as T-cell phenotype, function and persistence of the engineered infused cells as well as evaluation of candidate biomarkers and their correlation with clinical response to treatment. Data from such studies will be correlated to clinical outcome. These studies will be performed on bone marrow aspirates, serum and fractionated PBMC samples collected according to the Schedule of Procedures. All samples will be processed and/or frozen and analyzed either by central laboratory facilities contracted by the Sponsor, or by the Sponsor at the Sponsor's facilities.

Research studies conducted on blood samples may include:

- DNA analysis (qPCR) on PBMCs for engineered T-cell persistence and its association with response
- Flow cytometry on PBMCs to analyze immune cell subsets and persistence of engineered T-cells and their association with response

- Genomic sequencing to assess T-cell clonality through TCR Vbeta and Valpha sequencing and integration site analysis
- Determination of serum cytokine levels and their association with response
- Determination of soluble BCMA (sBCMA) in serum may be performed as a surrogate of disease burden
- As new technologies and data emerge, other assays relevant to the study objectives may be performed.

Bone marrow aspirate research studies may include:

- Flow cytometry on BMMCs to assess the frequency of immune cell subsets in tumor microenvironment and their correlation with treatment response. These data may be compared to frequency of immune cells in the blood with respect to treatment response
- DNA analysis of bone marrow aspirate (qPCR) to measure persistence of infused T-cells
- Assessment of mRNA levels of (RT-PCR, Next-Gen sequencing of RNA or Nanostring) of target antigens (NY-ESO-1 and LAGE-1a), other genes and immune cell markers including PD-1/PD-L1, and to associate their expression with response/resistance
- Genomic sequencing to assess T-cell clonality through TCR Vbeta and/or Valpha sequencing
- Analysis for target antigen (NY-ESO-1 and LAGE-1a) and immune cell infiltrates (by IHC/MultiOmyx) in relation to treatment response
- Next-Gen sequencing analyses to determine the evolution of the mutation profile of the tumor over the course of the therapy
- As new technologies and data emerge, other assays relevant to the study objectives may be performed.

If subjects have an ongoing clinical event, additional biopsy (for example skin, GI tract, BM) or blood (serum and PBMC) samples may be requested with the research objective of better understanding the etiology of the ongoing clinical event. For this purpose, the above described research tests may be performed on these samples.

7.5.1. Pharmacogenetics Sample

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

A whole blood sample for pharmacogenetics research may be obtained at any time throughout the study after eligibility is confirmed (refer to Table 3) in addition to any blood samples taken for the clinical study. The blood sample will be taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample. The blood sample can be taken at baseline or at any point during the treatment phase of the study providing the subject has given written informed consent for pharmacogenetics research. Details regarding sample collection are provided in the SPM.

Specific genes will be selected from areas of the genome (e.g., candidate genes) including areas associated with mechanisms underlying AEs. The candidate genes that may be investigated in this study include TGF-beta, TNF-alpha, IL-6, IL-10, and IFN-gamma.

7.5.2. Cytokine and Soluble Factors Analysis

Serum is collected at baseline, and at each visit post T-cell infusion (refer to the Schedule of Procedures in Section 7.3), to allow for measurement of cytokines in the blood. Serum is also collected from subjects with suspected CRS, samples being taken approximately every other day until symptoms are improving or an alternative diagnosis is confirmed (see Section 8.2). Details regarding serum collection are provided in the SPM.

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

Serum samples may also be used to investigate anti-TCR antibodies and soluble BCMA (sBCMA).

7.5.3. Bone Marrow Aspirates

A bone marrow (BM) aspirate is required during screening for confirmation of the NY-ESO-1 and/or LAGE-1a antigen expression.

As long as the multiple myeloma diagnosis has been histologically confirmed at an earlier date, no additional BM sampling will be mandated for eligibility screening.

Bone marrow samples (aspirates) are also required at baseline, Week 3 (or at Week 6 if the scheduled Week 3 infusion of pembrolizumab is delayed to Week 6 in Arm 2), Week 15, and at disease progression/end of treatment phase. In case of dry-tap, an aspirate must be repeated in another area for an appropriate bone marrow sample.

If the subject received systemic anticancer therapy between leukapheresis and lymphodepleting chemotherapy for disease control, then the timing of the BM sample at the baseline visit prior to lymphodepletion must also respect the wash-out periods of Exclusion criterion #21 (Section 4.2.2).

An aspirate is required at Week 3 (or at Week 6 if the scheduled Week 3 infusion of pembrolizumab is delayed to Week 6) to evaluate the infiltration of NY-ESO-1^{c259}T into the BM and for evaluation of the tumor microenvironment in relationship to baseline.

For subjects in Arm 2, the bone marrow aspirate must be taken prior to the pembrolizumab infusion on those visits at which both are scheduled.

Any bone marrow sampling at Week 24 and subsequent Q12wks visits are up to PI's discretion if not required for response assessment per IMWG criteria [Kumar, 2016]. A BM sampling is also required at the time of a CR to confirm the response per IMWG response criteria [Kumar, 2016]. The BM sample obtained at the time point believed to be the closest to maximum response will be analyzed for MRD. Whenever follow-up marrow collection is performed at physician discretion, sample may be obtained for research studies.

Additional details regarding the bone marrow aspirate collection are provided in the SPM.

BM aspirates may be used in particular to assess:

- target antigen expression (NY-ESO-1 and LAGE-1a)
- frequency of immune cells in the bone marrow microenvironment
- NY-ESO-1^{c259}T-cell persistence in the marrow (as described in Section 7.5.4),
- NY-ESO-1^{c259}T-cell clonality, and
- the depth of the clinical response by testing the presence of any MRD.

Assessment of MRD will employ a molecular method based on Next-Gen Sequencing (NGS) in which the specific immunoglobulin gene rearrangement present in the malignant plasma cell (PC) clone is identified in genomic DNA from a pre-therapy BM sample, then later tracked and quantified in post-therapy samples. That assay is the most sensitive known to date and is capable of detecting residual malignant PCs down to a frequency of 10^{-6}. MRD will be assessed at Week 15 (if relevant for subjects diagnosed with CR) the time of best clinical response.

The diversity of the T cell clones infiltrating the BM will also be investigated by NGS. Genomic DNA from BMMC or sorted NY-ESO-1^{c259}T cells will be used to measure the number and size of T-cell clones (V beta or V alpha) in relation to clinical response.

7.5.4. NY-ESO-1^{c259} T-cell Persistence

The primary research assays for the trial involve monitoring the persistence of infused engineered cells in the subjects in order to establish a correlation with potential therapeutic effect. Persistence is also monitored as a long-term safety measure (Section 10.1.3). Two well established methodologies will be used to measure the presence of transduced T-cells.

- Quantitation of NY-ESO-1^{c259} TCR^{+} cells by PCR of a vector-specific sequence in DNA extracted from PBMC
- Quantitation of NY-ESO-1^{c259} TCR expressing cells by flow cytometry (FCM) on frozen PBMC

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

A range of assays will be performed to further elucidate the phenotype and activity of the infused cells. The assays performed will depend upon availability of sample and clinical/scientific significance. The following assays may be performed (although analysis may not be limited to these assays; additional assays may be added as they become available).

- Phenotype analysis for determination of T-cell lineages
- Quantitation of the exhaustion and activation status of immune subsets from PBMC
- Quantitation of soluble factors reflecting in vivo function of NY-ESO-1^{c259} TCR^{+} T cells
- Anti-gene modified T-cell immune responses (tertiary assay)
- *Ex vivo* activity of transduced cells at different time points to assess potential anergy and/or exhaustion of those cells
- Analysis of gene expression profile to reflect activity of the cells.

7.5.6. Peripheral Blood Collection and Analysis

Recognizing that BM aspirates and biopsies cannot always be obtained, we set out to investigate whether alternative approaches can provide similarly valuable information. Therefore, in addition to BM aspirates, peripheral blood plasma will be collected in order to investigate both cell-free DNA (cfDNA) and exosomes.

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

- Estimation and genetic profiling of the global tumor burden (including expression of NY-ESO-1^{c259} mRNA and mutational profiling) from exosomes and cfDNA.
- Systemic assessment of the immune response (gene expression by cytotoxic and regulatory immune cells) from exosomes.

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

In accordance with FDA and EMA Guidances [FDA, 2020; EMA, 2009], all subjects enrolled in this trial are asked to consent to autopsy, and autopsies will be requested of the families for all subjects who die during participation in studies after administration of gene transfer agents. To ensure compliance, guidelines for performing an autopsy are provided in the SPM.

8. SUPPORTIVE CARE GUIDANCE

It is recommended subjects are treated under the care of a specialist with experience in the administration of hematopoietic stem cell transplant and/ or other cell and gene therapy. Subjects should be hospitalized for the T-cell infusion and for approximately 1 week of follow-up or until stable for discharge in a unit with staff experienced in the acute care of post-transplant subjects and the management of associated toxicities (e.g., cytopenias, CRS, aGVHD).

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

8.1. T-cell Infusion Symptom Management

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

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

8.2. Infection

Additional measures to treat and prevent infection are outlined below. In particular, fever and neutropenia should be aggressively managed as well as pre-emptive influenza therapy and other standard therapies for immunocompromised hosts, in accordance with institutional guidelines.

8.2.1. Pneumocystis carinii Pneumonia (PCP)

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

8.2.2. Herpes Simplex and Varicella Zoster

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

8.2.3. Cytomegalovirus

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

If a subject 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 8.7.

8.2.4. Hepatitis B Prophylaxis

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

8.2.5. Syphilis

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

8.2.6. Other Anti-Microbial Prophylaxis

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

8.3. Hematologic and Blood Product Support

Blood product support should be provided to maintain platelets >10 × 10^9/L, hemoglobin >8.0 g/dL (or in accordance with the institutional practices), and as clinically indicated. See AABB Guideline on platelet transfusion [Kaufman, 2015].

8.3.1. 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 x10^9/L (whichever is longer) must be irradiated. In addition, if a subject requires systemic

steroids or immunosuppression for the treatment of toxicity, irradiated blood products must be given until recovery of immune function.

8.3.2. Cytomegalovirus Screened Blood Products

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

8.4. Management of Autoimmunity

Subjects should be monitored throughout the trial for potential autoimmune reactions in response to the genetically engineered T cells that could include skin toxicity, liver toxicity, colitis, eye toxicity etc. If autoimmunity is suspected, the PI should be contacted and every attempt should be made to biopsy the affected organ to clarify whether the symptoms are related to the NY-ESO-1^{c259}T-cell therapy. If the subject 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.

8.5. Management of Cytokine Release Syndrome

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

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

Table 5 provides the recommended management of CRS according to grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels as described Section 7.5.2 as well

CRP levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 5 Management Guidelines for Cytokine Release Syndrome

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

1. Fever is defined as temperature ≥38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
3. Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.
4. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure.

5. Assessment and treatment to include history and physical, blood and urine cultures, imaging studies, administration of antimicrobial agents for concurrent bacterial infections, and for treatment of fever and neutropenia as per institutional practice; and antipyretics, analgesics as needed.
6. Given that prolonged fluid resuscitation without pressor use is associated with worse outcome and because early and aggressive supportive care, early use of vasopressors, and timely anti-cytokine therapy are paramount to mitigating life-threatening CRS.
7. Other immunosuppressor agents may be used, including TNFα and IL-1R inhibitors.

Source: [Lee, 2019]

Grade 1 CRS is defined as fever (≥38.0°C) with or without constitutional symptoms (Table 5). The constitutional symptoms of CRS, such as myalgia, arthralgia, and malaise, are by themselves nonspecific; however, when coincident with fever in the expected timeframe, the etiology of CRS is more likely.

Grade 2 CRS is defined as fever (≥38.0°C) with hypotension not requiring vasopressors and/or hypoxia requiring the use of oxygen delivered by low-flow nasal cannula (≤6 L/minute) or blow-by (Table 5).

Grade 3 CRS is defined as fever (≥38.0°C) with hypotension requiring 1 vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula (>6 L/minute), facemask, nonrebreather mask, or venturi mask not attributable to any other cause (Table 5).

Grade 4 CRS is defined as fever (≥38.0°C) with hypotension requiring multiple vasopressors (excluding vasopressin) and/ or hypoxia requiring positive pressure [eg, Continuous airway positive pressure (CPAP), bilevel positive airway pressure, intubation, mechanical ventilation] not attributable to any other cause. Outside of vasopressin, adding a second agent is a strong indication that the patient remains hemodynamically unstable after the first intervention. Such a scenario would be consistent with grade 4 CRS. Any use of positive-pressure ventilation constitutes a grade 4 CRS. Intubation of a patient without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not, by definition, grade 4 CRS. By extension, a patient experiencing seizures in which a compromised airway affects oxygenation and intubation reverses such deficits is not considered to have grade 4 CRS, because the seizure rather than CRS is the cause of the hypoxia. Furthermore, a patient who remains intubated for a neurologic cause is not considered to have CRS when the other signs of CRS have resolved.

By convention, grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome.

Subjects requiring immunosuppressive intervention may receive tocilizumab, steroids, or both [Davila, 2014; Lee, 2014; Lee, 2019]. Tocilizumab is a humanized anti-IL-6 receptor antibody that has been used to manage severe CRS (although it is not approved for this indication). Anecdotally, tocilizumab has produced rapid and complete correction of CRS with single doses [Maude, 2014]. Lee et al. [Lee, 2014; Lee, 2019] recommend administration of tocilizumab 4 mg/kg administered over 1 hour in adult subjects as the first-line treatment of severe CRS. Subjects may receive a repeat dose if clinical signs and symptoms do not improve within 24-48 hours.

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

Subjects unresponsive to tocilizumab or experiencing severe neurological symptoms (e.g. confusion, delirium, seizure) 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 antitumor effects of the ACT. However, in subjects with Grade 3 or 4 CRS associated with neurologic dysfunction without significant hemodynamic instability or other life-threatening symptomatology, consideration may be given to the use of corticosteroids as a preferred first-line immunosuppressive therapy. High doses (e.g. 2 mg/kg/day prednisone equivalent) may be required.

If CRS is suspected, a physician with expertise in the management of subjects following bone marrow transplant should be consulted. If high-dose corticosteroids are required, treatment should generally be continued for at least 5 days followed by tapering doses over several weeks.

Please refer to the most recent version of the product label for tocilizumab.

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

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

8.6.1. Diagnosis of GVHD

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

Table 6 Diagnosis of GVHD

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

Of 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 subjects following bone marrow transplant.

Bone marrow suppression is also a feature of transfusion-related GVHD. To minimize the possibility of transfusion-related GVHD, see Section 8.3.1 for guidance on irradiated blood products.

8.6.2. Grading of GVHD

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

Table 7 Stage of GVHD

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

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

Table 8 Grading of GVHD

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

[a]Staging is described above
[b]Mild, moderate, or severe decrease in performance status

8.6.3. Management of GVHD

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

If GVHD is suspected:

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

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

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

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

Table 9 Management of GVHD

Grade	Management Strategy
I	Subjects with grade I disease are not likely to require systemic treatment. Cutaneous GVHD may respond to topical steroid creams. Antihistamines may be helpful in subjects with pruritus. Subjects should be reviewed frequently for other organ manifestations of GVHD.
II	Treat skin symptoms with topical steroids. For GI symptoms - optimize antidiarrheal regimen, dietary restrictions, volume replacement and consider initiation of non-absorbable steroids. For refractory or progressive symptoms consider systemic steroids as outlined below.
III	For more severe or progressive symptoms consider systemic corticosteroids (e.g., methylprednisolone one (1) mg/kg per day*)
IV	Methylprednisolone two (2) mg/kg per day*
* The use of 'nonabsorbable' steroids (budesonide and beclomethasone) can be considered for acute intestinal GVHD in order to reduce the dose of systemic steroids	

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

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

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

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

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

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

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

- Absolute neutrophil count ≥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. Subjects are usually symptomatic on presentation, but some are detected incidentally when unexpected cytopenias are found on a routine blood count. The diagnosis of severe aplastic anemia is made in the setting of a hypocellular bone marrow when 2 of the following 3 blood counts are met: absolute neutrophil count <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 BM 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 BM recovery, the following measures should be implemented:

- Consult a physician with expertise in the management of aplastic anemia.
- Increase the frequency of CBCs as clinically indicated.
- Exclude other alternative etiologies such as other drugs, viral causes, etc.
- An early BM biopsy is recommended for clinical diagnosis, with a sample to be provided to the Sponsor for study. Refer to Section 7.4.10 (Correlative Studies and Research Assessments). Details on tissue collections, kit use and shipment information can be found in the SPM.
- A matched peripheral blood sample should be collected in parallel with the BM sample and provided to the Sponsor (refer to Section 7.4.10)
- 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/ID consultant(s). If high-dose corticosteroids are initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

Refer to Section 8.6 (Management of Graft-versus-Host Disease) regarding bone marrow suppression as a feature of GVHD.

8.8. Chemotherapy Symptom Management

Cyclophosphamide and fludarabine are used as pre-conditioning lymphodepletion chemotherapy in this study. Symptoms associated with the use of cyclophosphamide and fludarabine are included in the respective product labels. Refer to the most current product label and Section 1 for details of prohibited medications.

8.8.1. Management of Neutropenia

The cyclophosphamide and fludarabine chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF is recommended in all subjects. Filgrastim (G-CSF) should be used for management of neutropenia according to ASCO guidelines. G-CSF should be given 24 hours after the administration of chemotherapy and continued until reaching an absolute neutrophil count (ANC) of at least 2 to 3 × 10^9/L.

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

8.9. Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab

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 of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 10.

Table 10 Infusion Reaction Treatment Guidelines for Pembrolizumab

NCI CTCAE Grade	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 subject is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires therapy or infusion interruption but responds	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids	Subject may be premedicated 1.5 h (± 30 minutes) prior to infusion of

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 h	Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antianalgesic).
<u>Grades 3 or 4</u> Grade 3: Prolonged (ie, 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 ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine* IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. * In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		
Abbreviations: NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug		

8.10. Management of ICANS

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

CRES occurring within the first 5 days after immunotherapy may be concurrent with high fever and CRS symptoms. This form of CRES tends to be of shorter duration, lower grade (Grade 1–2, see Table 12), and is generally reversible with anti-IL-6 therapy. CRES presenting as delayed neurotoxicity with seizures or episodes of confusion can occur three or four weeks after CART 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.

8.10.1. Grading of ICANS

[Lee, 2019] have developed a new grading system for ICANS which incorporates use of a modified version of the CARTOX 10−point neurological assessment tool termed Immune Effector Cell-Associated Encephalopathy (ICE) (Table 11). Points are assigned for each of the tasks in the table which are performed correctly. Normal cognitive function is defined by an overall score of 10. The ICE should be used to monitor all subjects for ICANS.

Table 11 Immune Effector Cell-Associated Encephalopathy (ICE) assessment tool

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

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

The ICE score is used in grading of ICANS as presented in Table 12.

Table 12 Grading of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[1]	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.			
Depressed level of consiousness[2]				
Elevated ICP/ cerebral edema				

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Motor findings[5]	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.			
Seizure				

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

1. See Table 11 for ICE. A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
2. Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication)
3. Papilloedema grading is performed according to the modified Frisén scale.
4. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.
5. Tremors and myoclonus associated with immune effector cell therapies do not influence ICANS grading.

This table is based on Lee, 2019.

8.10.2. Monitoring for ICANS

Brain MRI (or CT Scan if MRI not feasible) should be obtained for all subjects at the time of screening. Baseline brain MRI should be obtained within 4 weeks prior to lymphodepletion.

ICE should be measured on the day of NY-ESO-1^{c259}T infusion prior to receiving treatment and then at least through Day 8 according to the schedule of procedures. If a subject is found to have 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.

8.10.3. Management of ICANS

The recommended management of ICANS should be based on toxicity grade. Table 13 provides guidance on the management of ICANS and should be implemented in accordance with institutional guidelines.

Grade 1 ICANS is primarily managed with supportive care as outlined below. For subjects requiring intervention beyond supportive measures, anti-IL-6 therapy should be

the first line treatment of for ICANS in the setting of CRS. In the setting of concurrent CRS, for Grades 1-3 ICANS additional doses of anti-IL-6 therapy should be considered before instituting corticosteroids since the use of systemic steroids may abrogate the effects of the T-cell therapy. For subjects with neurologic symptoms refractory to an initial dose of anti-IL-6 therapy, consider siltuximab for the second dose based on its mechanism of action directly against IL-6.

A neurology consultation should be obtained for all subjects with ICANS for thorough neurological evaluation, and recommendations for further testing such as EEG and neuroimaging as indicated in Table 13.

Table 13 Management of ICANS

Grade	Treatment
1	• Vigilant supportive care; aspiration precautions; intravenous (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 (CNS) depression • Evaluate for other contributing causes and treat accordingly • Neurology consultation including fundoscopic exam to assess for papilloedema • MRI of the brain with and without contrast (CT scan of the brain if MRI is not feasible). Further testing if indicated such as diagnostic lumbar puncture with measurement of opening pressure if increased intracranial pressure is suspected, or MRI of the spine if the subject has focal peripheral neurological deficits • Institute levetiracetam therapy and consider EEG if seizure activity is suspected • Consider anti−IL−6 therapy with tocilizumab 8 mg/kg[1] IVor siltuximab 11 mg/kg IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent CRS
2	• Supportive care and neurological work−up as described for grade 1 ICANS • Anti-IL-6 therapy if associated with concurrent CRS • Consider Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h if refractory to anti−IL−6 therapy, or for ICANS without concurrent CRS; once initiated continue corticosteroids until improvement to grade 1 ICANS and then taper • Consider transferring patient to intensive-care unit (ICU) if ICANS associated with grade ≥2 CRS
3	• Supportive care and neurological work−up as indicated for grade 1 ICANS • ICU transfer is recommended • Anti−IL−6 therapy if associated with concurrent CRS if not administered previously • Corticosteroids as outlined for grade 2 ICANS if symptoms worsen despite anti−IL−6 therapy, or for ICANS without concurrent CRS; continue corticosteroids until improvement to grade 1 ICANS and then taper • Stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure <20 mmHg should be treated corticosteroid regimen as per Grade 4 below. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 ICANS

Grade	Treatment
4	• Supportive care and neurological work−up as indicated for grade 1 ICANS • Consider neurosurgical consultation for patients with evidence of increased intracranial pressure • ICU monitoring; consider mechanical ventilation for airway protection • Anti−IL−6 therapy and repeat neuroimaging as described for grade 3 ICANS • High-dose corticosteroids continued until improvement to grade 1 ICANS and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days

[1] Maximum amount of tocilizumab per dose is 800 mg

Grade 1 ICANS. Grade 1 ICANS is defined as a score of 7-9 on the ICE assessment (Table 12). A patient with grade 1 ICANS may have a delay in responses or disorientation to time or place, mild inattention with difficulty in counting numbers backwards, or impairment of handwriting. There may be drowsiness, but patients awaken spontaneously, and when prompted, the patient should be able to complete most of the ICE assessment. Grade 1 ICANS may be seen during CRS waxing and waning with febrile episodes.

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

Grade 3 ICANS. Grade 3 ICANS is defined as a score of 0-2 on the ICE assessment (Table 12). Patients with grade 3 ICANS have severe global aphasia and are not speaking or following commands even when wide awake and therefore may be unable to complete any of the ICE questions. Alternatively, they may have excessive drowsiness and need tactile stimulus to attend to examiner. Any clinical seizure whether simple partial, complex partial or generalized, and any electrographic seizures would also meet criteria for grade 3 ICANS (Table 12, Table 13). If neuroimaging shows new focal or local edema this would also be categorized as grade 3 ICANS (Table 12, Table 13). However, intracranial hemorrhage due to coagulopathy or other causes with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading.

Grade 4 ICANS. Grade 4 ICANS is defined as patients who have a score of 0 on the ICE assessment (Table 12) due to being unarousable and unable to perform the ICE assessment. Stupor and coma may be seen; the stuporous patient only responds by grimacing or drawing away from vigorous or repetitive tactile stimuli and the comatose patient is unarousable and/or unresponsive. This depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication), which is often a complicating factor in sick patients with CRS. Some patients may require intubation for

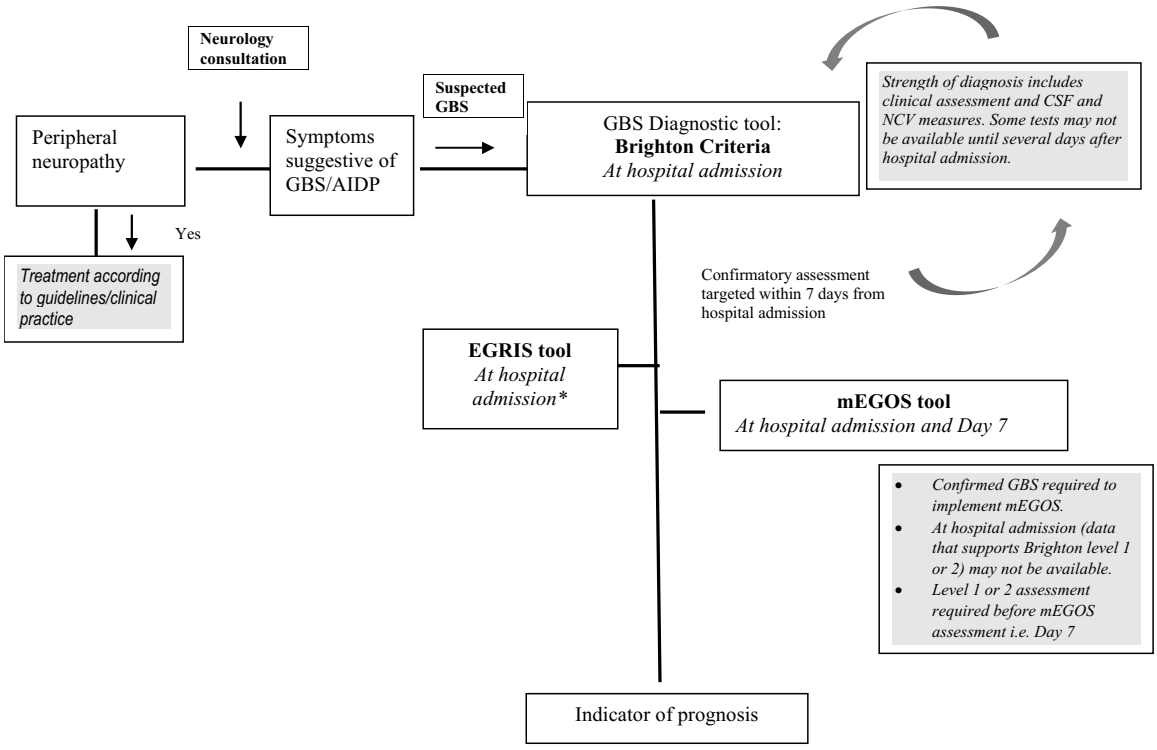
airway protection. In addition, any patient having prolonged or repetitive clinical or subclinical electrographic seizures without return to baseline in between, or deep focal motor weakness such as hemiparesis or paraparesis would be considered to have Grade 4 ICANS. Patients with symptoms and signs of elevated ICP such as projectile vomiting with headache, depressed consciousness, cranial nerve VI palsies, papilledema, Cushing's triad of bradycardia, hypertension and respiratory depression, decerebrate or decorticate posturing, or diffuse cerebral edema on head imaging would also be considered to have grade 4 ICANS.

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

8.11. Management of Guillain-Barré Syndrome (GBS)

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

Figure 3 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.

8.11.1. Neurological Symptoms

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

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

- Areflexia (or decreased tendon reflexes) in weak limbs

Additional symptoms

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

8.11.2. 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

8.11.3. Erasmus GBS Respiratory Insufficiency Score (EGRIS)

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

Parameters required at hospital admission:

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

8.11.4. Modified Erasmus GBS Outcomes Score (mEGOS)

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

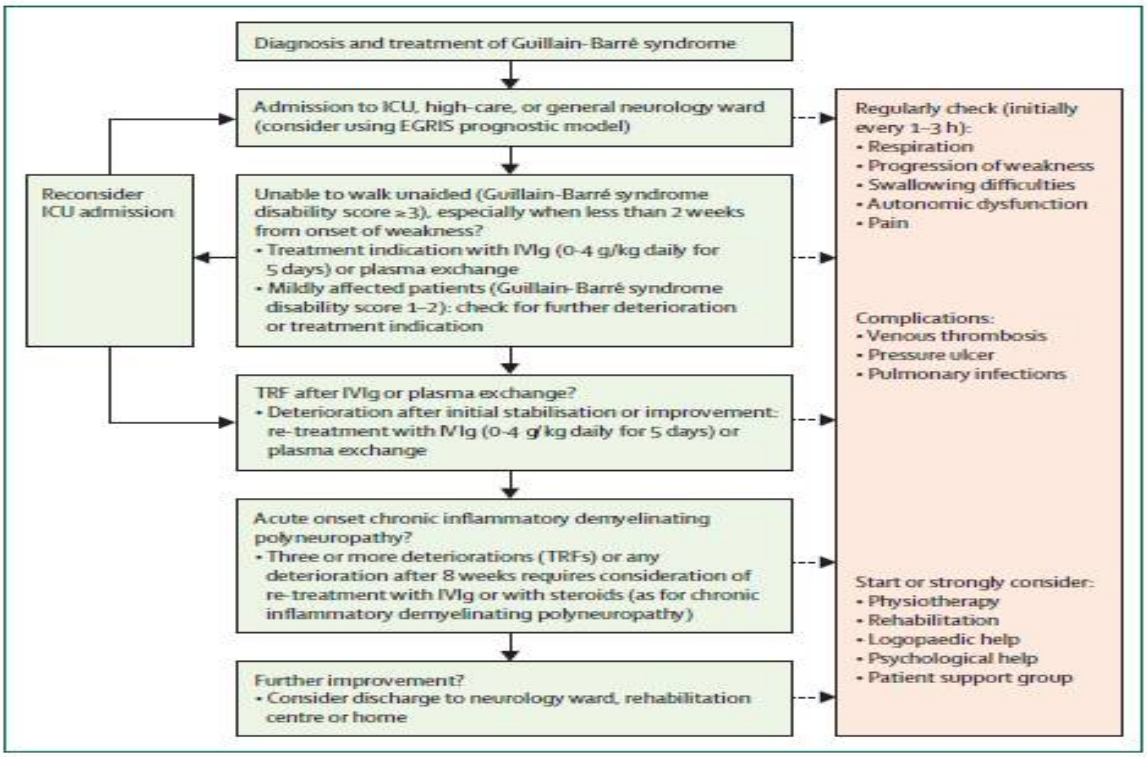
- Age at onset
- Preceding diarrhoea (in 4 weeks preceding onset of weakness)

- Medical Research Council sum score

8.11.5. 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.).

9. RECORDING ADVERSE EVENTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and is mandated by regulatory agencies worldwide. The Sponsor has established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of all safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures. The Investigator and their designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. Individual AEs should be evaluated by the Investigator and reported to

the Sponsor as appropriate. This includes the evaluation of its intensity, the causality between the IP and/or concomitant therapy and the AE, and seriousness.

The Sponsor has to keep detailed records of all AEs reported by the Investigator(s) and to perform an evaluation with respect to causality, seriousness, and expectedness.

9.1. Time Period for Collecting Adverse Event and Serious Adverse Event Information

AEs and SAEs will be collected at the time points specified in Table 3 for the treatment phase of the study.

- During Part 1 of the study: Any SAEs or AEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or leading to early withdrawal, will be collected in the AE section of the CRF from the time a subject signs the informed consent for target expression screening. All other relevant events that begin before the start of leukapheresis but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.
- During Part 2 of the study: Any SAEs or AEs assessed as related to study participation (e.g., leukapheresis, other 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. All other relevant events experienced or occurring while the subject was undergoing bridging or intermediate therapy (i.e., anti-cancer therapy, including experimental regimens under another study protocol, even if with another Sponsor) will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section, at the time of the evaluation of study eligibility for part 3 (lymphodepletion/treatment).
- During Part 3 Arm 1 of the study: All SAEs will be collected from the Baseline Visit until the end of study. Regardless of study end for a subject, all SAEs must be collected through 90 days following T-cell infusion, or 30 days following T-cell infusion if the subject initiates new anticancer therapy, whichever is earlier. All AEs will be collected from the Baseline Visit until 30 days following cessation of study treatment OR the end of study, whichever is later
- During Part 3 Arm 2 of the study: All AEs and SAEs will be collected as for Arm 1 or until 30 days for AEs and 90 days for SAEs following cessation of pembrolizumab treatment (30 days only if subject initiates new anticancer therapy), whichever is the longest period of collection. For subjects who received pembrolizumab and who have an allo-SCT within 24 months of last dose of pembrolizumab, specific and medically important adverse events will be collected for 18 months from the date of the transplant (see Section 9.5).

- During LTFU (15 years post T-cell infusion) subjects will only be monitored for potential gene therapy-related delayed adverse events (see Section 9.4 and the LTFU protocol GSK208750 [ADP-0000-002]).
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Any SAE, including death, brought to the attention of an Investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.
- Events of special interest (Section 9.13) will be reported to the Sponsor (or designee) immediately and under no circumstance should this exceed 24 hours.

9.2. Definition of Adverse Event

In accordance with the ICH, an AE is any untoward medical occurrence in a subject or clinical investigation subject who receives a pharmaceutical product. The event does not necessarily have a causal relationship with study treatment to be an AE. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP. Pre-existing conditions which worsen during the study are to be reported as AEs. Progression of the cancer under study is not considered an AE unless it is considered to be drug-related by the Investigator (see Section 9.5).

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

All AEs should be followed until:

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

On completion of the subject from the treatment portion of the study, or withdrawal from the study, serious or severe AEs will be followed until one of the above criteria is met. SAEs related to IP will continue to be recorded and monitored into LTFU at any time (Section 9.4).

9.2.1. Assessment of Intensity

Adverse events will be graded according to the NCI-CTCAE v 4.0. Refer to Section 8.5 and Section 8.6.2 for specific grading of CRS and GVHD respectively.

The Investigator will assess intensity of all AEs using this five-point scale (Grade 1-5) and record on the eCRF.

AEs not specifically listed on the NCI-CTCAE should be graded according to Table 14 :

Table 14 Grading of AEs not specified in NCI-CTCAE v4.0

NCI-CTCAE Grade	Equivalent to	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; minimal medical intervention is indicated.
Grade 3	Severe	Incapacitating with inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the subject at direct risk.
Grade 4	Life-threatening/ disabling	An immediate threat to life that requires urgent medical intervention.
Grade 5	Death	AE resulting in death.

Abbreviations: AE = adverse event; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events

9.2.2. Assessment of Causality

The Investigator will assess the causal relationship between the AE and IP according to his/her best clinical judgement. An assessment of possibly/probably/definitely related is meant to convey there is evidence of a causal relationship, not that a relationship cannot be ruled out. The Investigator should consider alternative causes such as natural history of the underlying disease, lymphodepleting chemotherapy, concomitant medications, and other risk factors when making an assessment. The following scale will be used as guidance:

- **Not related** – The subject did not receive the IP; the temporal sequence of the AE onset relative to administration of the IP is not reasonable; or there is another obvious cause of the AE.
- **Possibly related** – There is evidence of exposure to the IP; the temporal sequence of the AE onset relative to T-cell infusion is plausible; or the AE could have been due to another equally likely cause.
- **Probably related** – There is evidence of exposure to the IP; the temporal sequence of the AE onset relative to T-cell infusion is plausible; the AE shows a pattern consistent with previous knowledge of the IP; or the AE is more likely explained by the IP than any other cause.
- **Certainly related** – There is evidence of exposure to the IP; the temporal sequence of the AE onset relative to T-cell infusion is plausible; the AE shows a pattern consistent with previous knowledge of the IP, or the AE is most likely explained by the IP and any other cause is improbable.

The Investigator may change his/her opinion of causality if additional information is received and amend the AE eCRF accordingly. The Investigator causality assessment is one of the criteria GSK use to determine regulatory reporting requirements for an SAE.

9.3. Reporting Serious Adverse Events (SAEs)

An SAE is any adverse event that:

- Results in death (results in death; NOTE: death is the outcome, not the event).
- Is life-threatening; (NOTE: the term "Life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant disability.
- Is a congenital anomaly/birth defect.
- Is clinically significant or requires intervention to prevent one or the outcomes listed above.

Medical and scientific judgment should be exercised in deciding if an AE is of significant enough medical importance to be classified as serious outside the above definitions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department, would typically be considered serious. In this case event will be reported using the serious criteria of clinically significant or requires intervention.

Additional protocol-defined criteria

- Any Grade ≥3 CRS or GVHD, and all cases of Guillain-Barré syndrome or acute inflammatory demyelinating polyneuropathy must be reported as an SAE within 24 hours.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

An SAE must be reported to GSK within 24 hours of the study personnel's discovery of the event by completing an SAE Worksheet and submitting by e-mail to both mailboxes: PPD and PPD, or by fax: PPD PPD. The SAE eCRF form within the electronic data capture (EDC) system must also be completed.

For the time period beginning at signature of Screening ICF through 90 days following cessation of pembrolizumab, or 30 days following cessation of pembrolizumab if the subject initiates new anticancer therapy, whichever is earlier, any SAE, or follow-up to an SAE, including death due to any cause other than progression of the cancer under study, whether or not related to the Sponsor's product, must be reported to the Sponsor.

The SAE eCRF must be completed by the Investigator with as much information as is available. The minimum reporting criteria for an SAE include:

- Identifiable subject (Subject ID)
- Event that is identified as serious (SAE term)
- Suspect medicinal product
- Relationship to IPs
- Identifiable reporting source (PI acknowledgment of the report and his/her signature is required).

The Investigator will assess the causal relationship between the SAE and IP(s) according to his/her best clinical judgement. The Investigator will also assess the causal relationship between the SAE and the lymphodepleting chemotherapy.

Further details can be found in the SPM.

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

Due to the nature of the treatment, subjects are required to be followed for up to 15 years after treatment with genetically modified T cells according to FDA and EMA guidance [FDA; 2020; EMA, 2009]. Subjects will be followed according to the schedule outlined in the LTFU protocol GSK208750 (ADP-0000-002). Certain events in this protocol are identified as delayed AEs and should be marked as delayed AEs in the eCRF.

Delayed AEs are defined as those events that fall into one or more of the 6 categories listed below and which occur either more than 108 weeks following NY-ESO-1^{c259}T cell infusion or after disease progression, whichever occurs first. In the event a subject has not progressed by 108 weeks following GSK3377794 infusion, delayed AEs will be collected in Interventional Phase of study. Delayed AEs which occur post progression will be collected as part of the LTFU phase of the current study or in the LTFU Study (208750), contingent upon formal transfer of subject to Study 208750.

- New malignancies
- New incidence or exacerbation of a preexisting neurological disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of an immune-related hematologic disorder
- Serious infections (including opportunistic)

- Unanticipated illness or hospitalization deemed related to gene modified cell therapy
- Specific events outlined in Section 9.5 for subjects who received pembrolizumab and had allo-SCT

A detailed narrative description of the event should include the date of diagnosis and the nature of the diagnosis for all AEs. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites. If a new malignancy is recorded in a vector target cell type, tumor cells will be evaluated for vector sequences. If the tumor is positive for vector sequences or the surrogate sample is positive for vector sequences and is confirmed in accordance to this protocol, clonality analysis will be performed. If no evidence of oligo-or monoclonality is observed, a summary report of any and all analysis for the pattern of vector integration will be assembled and submitted within the annual report of the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. If evidence of oligo- or monoclonality is observed, an information amendment will be submitted within 30 days to the INDs listed on this protocol under which the subject(s) evaluated originally received their treatment. Adverse events should be recorded in the eCRF using a diagnosis or possible diagnosis, and rated for intensity, causality and seriousness. If photographs are requested by the Sponsor of e.g. a rash AE, the subject will sign a Medical Photograph Release prior to any photographs being taken. Suspected unexpected serious adverse reactions (SUSARs) deemed related to the gene modified cells will be reported to the Regulatory Agencies and shared with Investigators as necessary in the form of Investigational new drug safety reports (INDSRs).

All AEs should be followed until:

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

9.5. Follow-up post Allogenic Stem Cell Transplantation for Subjects Who Received Pembrolizumab

For subjects who received pembrolizumab and who have an allogeneic stem cell transplant (allo-SCT) within 24 months of last dose of pembrolizumab, specific events (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 (acute and/or chronic)
- Veno-occlusive disease
- Febrile syndrome (a steroid-requiring febrile illness without an infectious cause)
- Encephalitis

Additional medically important adverse events post- allo-SCT may be reported at the investigator's discretion. This follow-up can be carried out under the current protocol or under the LTFU protocol.

9.6. Progression of Underlying Malignancy

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

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

9.7. Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor has legal obligations for expedited reporting of certain events to Regulatory Authorities, IRBs/ Research Committees (RC), and other study subjects. GSK will comply with all GCP and country specific regulatory requirements relating to safety reporting to the Regulatory Authorities, IRBs/RCs, and Investigators.

Investigator safety reports for suspected unexpected serious adverse reactions (SUSARs) are prepared and distributed according to local regulatory requirements and GSK policy. These safety reports are forwarded to Investigators as necessary in the form of INDSRs.

An Investigator who receives an INDSR describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and notify their IRB/RC if appropriate, in accordance with local requirements.

On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor will submit detailed records of all AEs which are reported to him by the relevant Investigator(s).

9.8. Cardiovascular and Death Events

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

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

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

Definition of Cardiovascular Events

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

9.9. Pregnancy

There is no preclinical or clinical trial data of NY-ESO-1^{c259}T in pregnant women; however, there is a reasonable but unproven likelihood that this intervention may be significantly embryotoxic or even an abortifacient given the underlying biology of the target. The effects on breast milk are unknown; therefore, breastfeeding should be discontinued for the duration of the study, starting at the first dose of chemotherapy and for at least 12 months after receiving the T-cell infusion, or 4 months after there is no evidence of persistence/gene modified cells in the subject's blood, whichever is longer.

Pregnancy (or pregnancy of a male subject's partner) is not considered an AE/SAE unless there is reason to believe that the pregnancy may be the result of failure of the contraceptive being used due to interaction with any of the IPs. However, the Investigator shall report all pregnancies immediately to the Sponsor. A woman who becomes and remains pregnant during the study will be discontinued from the treatment phase as exposure to radiation from imaging studies would be contraindicated in this setting. The subject would enter into LTFU. The outcome of the pregnancy must also be reported to the Sponsor. The contraception and pregnancy guidelines in Section 6.3.3 should continue to be followed during LTFU.

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

9.10. Preexisting Condition

A preexisting condition is one that is present at the start of the study during screening. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the treatment phase.

9.11. Laboratory Test Abnormalities as Adverse Events

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

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

9.12. Overdose

For this trial, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.13. Adverse Events of Special Interest

Selected non-serious and serious AEs are also known as events of special interest (ESI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until enrollment, any ESI , or follow-up to an ESI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or that is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Following enrollment, ESIs will be reported to sponsor within 24 hours for the same period as AEs and SAEs (see Section 9.1). Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the SPM.

ESI for this trial include:

- Cytokine release syndrome (CRS) [Note: Grade 3 or higher should be reported as SAE within 24 hours]
- Graft vs host disease (GvHD)
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grade 1 persisting beyond 24 hrs or associated with concurrent CRS; or Grade 2 or higher
- Guillain Barre syndrome (GBS) including acute inflammatory demyelinating polyneuropathy (AIDP) [Note: all cases must be reported as SAEs within 24 hours]
- Pancytopenia/aplastic anemia if any of the below events occur:
  - Occurs after the bone marrow reconstitution following the lymphodepletion regimen
  - Any Grade 3 or 4 cytopenia following lymphodepletion lasting more than 2 weeks with G-CSF support
  - Requiring transfusion support (e.g. platelets or RBC) lasting more than 2 weeks following lymphodepletion
- Treatment-related inflammatory response at tumor site(s)

- An overdose of pembrolizumab, as defined in Section 9.12, 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 3× the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2× the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2× 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 found in the SPM.

9.14. Timelines for Safety Reporting

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 Hours	Pregnancy Notification Form	2 Weeks	Pregnancy Followup- Form
AESI	24 hours	AESI data collection tool (plus SAE if applicable – see Section 9.13.)		Update AESI date collection tool

10. SAFETY MONITORING

10.1. Monitoring and Management of Replication-Competent Lentivirus (RCL)

Replication Competent Lentivirus (RCL) is a theoretical risk associated with the use of lentiviral vectors; no RCL has ever been detected in vitro or in vivo. The risk is derived from the detection of replication competent retrovirus (RCR) during the use of early γ retroviral vector packaging systems which were inadequately designed to avoid recombination events between the vector and packaging components [Miller, 1990]. Updated γ retroviral packaging systems have not been associated with RCR. However, in a study with Rhesus monkeys, three out of 10 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 subjects post T-cell infusion with any product involving a retrovirus [FDA, 2006; FDA; 2020; FDA, 2010; EMA, 2009].

A RCL may be generated during the production phase or subsequently after introduction of vector transduced cells into the subject. RCL may be generated 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 an RCL by recombination with an endogenous virus (i.e., HIV) in the subject following infusion of the vector product remains a theoretical possibility. The consequences of such recombination events could be neutral, could reduce the replication rate or pathogenicity of the subject's endogenous virus, or could increase the replication rate or pathogenicity of the subject's endogenous virus. Since the development of a strain with increased pathogenicity would pose greater risk to both the subject and their close contact(s), periodic monitoring for RCL is conducted during the course of the trial and during the 15-year follow-up.

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject [FDA, 2006; FDA; 2020; EMA, 2009]. However, because the probability and characteristics of an RCL are unknown, no concrete plans have been put in place. As of the writing of this protocol it is agreed the subject must be isolated until an understanding of how to manage the concern becomes clear.

The following approaches have been discussed for subject management:

- Provide targeted antiretroviral therapies based on genotyping of the RCL.
- Intensive follow-up of subject in consultation with gene therapy experts, Study Investigators, HIV physicians, FDA, other regulatory agencies, and NIH.

10.1.1. 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 cell product, whereby RCL testing will be performed by or under the direction of the manufacturing facility responsible for manufacturing and release of the vector.
- Subject PBMCs will be collected prior to infusion of transduced T cells and then at 3, 6, and 12 months post treatment. If these tests are negative at all time points during the first year, PBMC samples will be collected annually and archived for up to 15 years post T-cell infusion or until assessments for persistence have ended (Section 10.1.3.1); however, if VSV-G DNA copies are detected at any time point in the first year post-infusion, the safety monitoring protocol (Section 10.1.2) will be triggered. Subject samples will continue to be tested for VSV-G DNA copies until VSV-G DNA copies are not detected for 3 consecutive annual assessments, then subject samples will be collected annually until 15 years post-infusion and archived at GSK's centralized biorepository or until assessments for persistence have ended (Section 10.1.3.1).

10.1.2. Safety Monitoring Results

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

Response to potential outcome of second VSV-G DNA test:

- If the second test is negative, then subject samples will continue to be tested for VSV-G DNA copies until VSV-G DNA copies are not detected for 3 consecutive annual assessments, at which time the subject samples will be collected and archived annually until year 15.
- If the second test is positive, infusions for all subjects receiving T cells modified with the same vector lot will be postponed. The subject with the confirmed positive VSV-G signal will be scheduled for leukapheresis and a biological RCL test will be performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product [Manilla, 2005].

If the biological RCL test is positive, all infusions using NY-ESO-1^{c259}T in the interventional protocol(s) will be halted. An action plan will be discussed with FDA and other regulatory authorities and experts as appropriate. Additional subjects will not be

treated with NY-ESO-1^{c259}T cells until such time as a plan is completed, reviewed, and agreed upon.

If the biological RCL test is negative, infusions for all subjects can resume.

10.1.3. Persistence Testing and Monitoring for Insertional Oncogenesis

Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA and EMA guidances [FDA, 2006; FDA; 2020; EMA, 2009]. Insertional oncogenesis is a theoretical risk in T cells transduced with a lentiviral vector. T cells appear resistant to transformation by integrating viruses [Cattoglio, 2010; Newrzela, 2008]. However, there are cases of oncogenesis with γ-retroviral transduced stem cells. Four of nine subjects with X-linked severe combined immunodeficiency (SCID-X1) treated with retrovirus transduced stem cells were found to have insertion near the LMO2 proto-oncogene promoter, leading to aberrant transcription and expression of LMO2 which resulted in acute T-cell lymphoblastic leukemia [Hacein-Bey-Abina, 2003; Hacein-Bey-Abina, 2014]. Additionally, two subjects treated for X-linked chronic granulomatous disease (X-CGD) with retroviral transduced stem cells demonstrated insertional activation of the EVI1 transcription factor which resulted in genetic instability, monosomy 7 and clonal progression toward myelodysplasia [Stein, 2010].

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

PBMC samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects prior to infusion of transduced T cells and then at 3, 6 and 12 months post-infusion, then every 6 months until 5 years post-infusion and every year from year 6 post infusion in accordance with the FDA and EMA guidances [FDA, 2006; FDA; 2020; EMA, 2009]. The samples will be tested using a PCR-based method to detect the presence of the WPRE or the Psi gene, both of which are part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion greater than 1% PBMCs test positive for vector sequences, the subject's PBMCs will be evaluated for integration site analysis (see Section 10.1.3.2). If no gene modified cells are detected for three consecutive assessments post-infusion, and the subject is more than 5 years post-infusion, no further monitoring of PBMCs is required and collection of samples for persistence may be discontinued. NOTE: Samples for RCL must continue to be collected and archived up to 15 years post-infusion. Hematology and chemistry assessments may also be discontinued. The subject will continue to be followed by the Investigator for up to 15 years post-infusion. The Investigator will be the primary physician responsible for continued follow up of the subject for the duration of LTFU whenever possible. If contact with the investigator becomes no longer feasible, follow up can be transitioned to a local physician, preferably an oncologist.

10.1.3.2. Testing for Insertional Oncogenesis

If persistence, as detected by the presence of a vector sequence (Psi DNA copies), is present in >1% of PBMC at 1 year or beyond post-infusion, DNA from the subject's

PBMCs will be sent for integration site analysis. Integration site analysis will also assess the possibility of insertional oncogenesis.

If there is clonal dominance in the genetically modified T-cell population (either monoclonality or oligoclonality) the persistence assessment will be repeated within 3 months on a new sample. If the repeated analysis demonstrates: 1) persistent monoclonality, 2) evidence of insertional oncogenesis or 3) clonal expansion (an increase in percent predominance of a clone), there will be a review by the Sponsor to develop a monitoring plan specific to the health care risk, and/or strategies to inform appropriate subjects, Investigators, and regulators of the findings. If the integration site analysis indicates polyclonality of the genetically modified T-cell population, then screening will continue as scheduled.

10.2. Management and Monitoring for Demyelinating Neuropathy and other Neurological events

Obtain a neurological consultation for subjects with Grade 2 or higher neurologic events of a ≥ 7-day duration. Subjects who develop signs and symptoms consistent with GBS must be evaluated by a neurologist according to diagnostic guidance for GBS [Fokke, 2014] to provide expert recommendations to guide appropriate diagnostic workup such as EMG, lumbar puncture, infectious panel to guide management and follow up.

10.3. Safety Review Team

A SRT will be implemented in this study. In line with routine pharmacovigilance, a GSK SRT will review safety data, including clinical laboratory parameters and AEs, at appropriate intervals during the period of study conduct. Recommendations on study modification, halting the study and/or pausing enrollment will be provided by the SRT. An SRT charter, defining roles and accountabilities and the process for safety review and meeting frequency, will be available.

10.3.1. Mandated Study Pause Due to GBS

The occurrence of any event of GBS will mandate a pause in enrollment and stopping treatment for all subjects within the GSK3377794 studies. The case must be diagnosed by a neurologist as GBS according to diagnostic guidance for GBS [Fokke, 2014].

11. STATISTICAL AND DATA ANALYSIS

The objective and endpoints for this study are described in Section 2. This section focuses on key aspects for the analysis and reporting of the primary and secondary efficacy and safety endpoints. Details for the analysis of all endpoints will be provided in the RAP.

For this pilot study the objective is to describe the safety/tolerability and antitumor activity of monotherapy (NY-ESO-1^{c259}T alone; Arm 1) and combination therapy (NY-ESO-1^{c259}T plus pembrolizumab; Arm 2). The study is not powered to compare efficacy or safety between the arms and therefore no formal statistical comparisons between arms is planned.

Key endpoints for safety include all AEs, AEs of special interest, clinical and laboratory assessments, long-term safety follow-up, and subject disposition.

Key endpoints for antitumor activity include ORR and DOR, as well as PFS and OS.

The primary analysis will be performed after enrollment is complete and all the enrolled subjects that will receive NY-ESO-1^{c259}T have done so and of those: all have been followed up for at least 6 months after NY-ESO-1^{c259}T infusion or have progressed or died or were withdrawn from the study.

The final analysis will be conducted after enrollment is complete and all the enrolled subjects that will receive NY-ESO-1^{c259}T have done so and of those: all have completed the study (as defined in Section 4.4) or died or were withdrawn from the study.

If it is believed the primary analysis will occur within 6 months of the final analysis, the primary analysis may not be performed such that there will only be the final analysis.

A description of the key safety and efficacy analyses follows. The details for the safety and efficacy analyses will be described prospectively in the RAP. Analysis of exploratory endpoints, sensitivity analyses, and the handling of missing values including censoring rules will be described in the RAP.

11.1. Study Populations

To ensure robustness and a more comprehensive understanding of the data, the following populations will be evaluated using descriptive statistics for safety and anti-tumor activity:

Screened Population: All subjects who were screened for eligibility.

Intent-to-Treat (ITT) population: All subjects who underwent leukapheresis. The ITT population will be the primary analysis population for safety endpoints.

Modified ITT (mITT) population: All subjects who received NY-ESO-1^{c259}T. The mITT population will be the primary analysis population for efficacy endpoints.

As-Treated (AT) population: All ITT subjects per the actual treatment received. This population will only be assessed if subjects do not receive the assigned therapy.

Additional analysis populations may be defined in the RAP.

If the ITT and mITT populations are identical at the end of the trial, then only the ITT population will be summarized. TLTs will only be evaluated for eligible subjects assigned to Arm 2.

All data analyses will be conducted within arm, unless otherwise noted.

Analyses grouped by use of BCMA as prior intermediate therapy may be presented if there are sufficient subjects.

11.2. Interim Analysis

Interim analyses to inform internal decision making may be performed for each arm after enrollment to the arm is complete and all the enrolled subjects in that arm who will

receive NY-ESO-1^{c259}T have done so and of those: all have completed at least three disease assessments since infusion or have progressed (and if progressed prior to the Week 9 visit have been followed up for safety for a minimum of 9 weeks following T-cell infusion) or have died or were withdrawn from the study.

The sponsor will do period data looks to inform internal decision making. This may include an analysis once all Arm 1 subjects satisfy the criteria for the primary analysis.

11.3. Sample Size and Assignment of Study Arms

Sample size is based on clinical judgement. Based on the known safety profile of NY-ESO-1^{c259}T, a sample size of 10 subjects per arm is considered clinically sufficient for evaluation of safety and tolerability of each arm in this pilot study. The study is not powered to compare efficacy or safety between the treatment arms. Eligible subjects will be assigned to either Arm 1 or Arm 2 prior to leukapheresis. Enrollment of Arm 1 will be completed before continuing enrollment of subjects to Arm 2. Subjects who do not receive NY-ESO-1^{c259}T for any reason may be replaced. Enrollment to Arm 2 will be paused after the third subject enrolled in Arm 2 has started lymphodepletion (Section 3.3.1). Enrollment may be paused again later in the trial if a potential safety finding emerges in either arm at any time (Section 4.7).

The overall response rates (ORR) in subjects with RRMM who have received a median of 5 prior therapies ranges from 23.7% to 33% where the midpoint is 28.35% (see Section 16.5). Further development of NY-ESO-1^{c259}T for RRMM in monotherapy or in combination with pembrolizumab may be stopped due to futility if there is sufficient evidence from the corresponding arm that the true ORR is less than 40%.

The hypothesis for ORR is H_0: 20% vs. H_1: 40%. The sample size of 10 subjects treated per arm allows for early stopping of further development of that arm due to futility if the posterior probability that the ORR is less than 40% is >99%. This is equivalent to observing 0 or 1 responders out of the 10 treated subjects. Additionally, if the true ORR is 20%, the probability of observing 1 or 0 responders out of 10 treated subjects is 38% and if the true ORR is 40% the probability of observing 1 or 0 responders out of 10 treated subjects is 5%. These decision rules are for guidance only and the final decision for stop for futility will be determined on totality of data.

If supported by safety and efficacy results, additional subjects may be enrolled to confirm the safety and efficacy via a protocol amendment or as part of a separate protocol. Two or more confirmed responses (CR or PR) out of 10 treated subjects may provide sufficient efficacy evidence to expand and enroll additional participants. This will serve as guidance for final decisions regarding enrollment of additional subjects, which will be based on a review of the totality of the data.

11.4. Statistical Methods for Safety Parameters

Safety will be evaluated both during the trial and at the planned analyses.

11.4.1. TLT Evaluation for Arm 2

Bayesian methods will be employed to assess safety throughout the study. The advantages of a Bayesian framework in a small safety-oriented study is that in addition to being able to incorporate prior information, it also allows one to make evaluations without relying on large sample theory.

11.4.1.1. TLT Rate Definition

The TLT rate is defined as the proportion of subjects at any time during the study who have at least one TLT. The TLT rate, p, will be evaluated in the combination arm only, in an ongoing manner. Statistical evaluations for the TLT rate will be made after a minimum of n=3 subjects have been infused with NY-ESO-1^{c259}T, received their first dose of pembrolizumab and cleared the TLT 3-week assessment period (as described in Section 3.3.2). TLT rates in excess of 0.33 have been identified as clinically concerning. Bayesian methods are used to continually evaluate the strength of evidence that the subjects will experience a TLT rate > 0.33 if the arm were to proceed to treat N_{max}=10 subjects.

The number of subjects with at least one TLT, X, in n subjects at any time during the trial is assumed to follow a binomial distribution, B(n, p). Further, assuming a fairly non-informative prior distribution, i.e., a beta(0.18, 0.82) for the TLT rate, the posterior of the TLT rate follows a beta(0.18+x, 0.82+n-x) distribution. This then means that the future number of TLTs, Y in m = N_{max} - n follows a beta-binomial (m, 0.18+x, 0.82+n-x) distribution. Using the methods described by Lee and Liu [Lee, 2008] (with θ=0.9), the predictive probability that the TLT rate exceeds 0.33 at N_{max}, can be computed as subjects accrue. This probability will be assessed at a threshold of 0.50.

11.4.1.2. Bayesian Predictive Probabilities for N_{max} = 10

As described in Section 3.3.5, only the combination arm will be evaluated for TLTs. Given n and N_{max}, the above predictive probabilities can be computed as X varies from 0 to n, and the threshold for safety considerations corresponds to the first time the predictive probability exceeds 0.5. The corresponding values of X subjects with TLTs out of n (≥3) are described below.

Table 15 below provides the predictive probabilities where the gray shaded blocks are the smallest X for a given n where the predictive probability exceeds 0.50.

Table 15 Predictive Probabilities for N_{max} = 10

	X=0	X=1	X=2	X=3	X=4	X=5	X=6	X=7	X=8	X=9
n=3	0.0017	0.115	0.566	0.9426	NA	NA	NA	NA	NA	NA
n=4	0.0002	0.0341	0.3083	0.7812	0.9842	NA	NA	NA	NA	NA
n=5	0	0.0059	0.1255	0.5447	0.9165	0.9974	NA	NA	NA	NA
n=6	0	0	0.0298	0.2932	0.7678	0.9813	1	NA	NA	NA
n=7	0	0	0	0.0956	0.5305	0.9279	1	1	NA	NA
n=8	0	0	0	0	0.2406	0.7954	1	1	1	NA
n=9	0	0	0	0	0	0.518	1	1	1	1

For example, when n=3, the first time the predictive probability exceeds 0.50 is when 2 subjects out of 3 experience at least one TLT. The predictive probability in this situation that the TLT rate exceeds 0.33 at N_{max} = 10, is 0.5660, which exceeds 0.5. Clearly if 3 of 3 subjects experience TLTs, this would also lead to pausing enrolment. Therefore, if at least 2 out of 3 subjects experience a TLT, the trial should be paused to evaluate safety further. Similarly, the trial may be paused for safety evaluation if (at least) 3 out of 4 or 5, 4 out of 6 or 7, or 5 out of 8 or 9 subjects have at least 1 TLT.

Further, if the threshold exceeds 0.5 as described above, other supportive information may be computed. For example, the predictive probability distribution may also be evaluated to calculate the probabilities associated with specific outcomes. For e.g., if 4 subjects have TLTs out of 7, then the beta-binomial (3, 4.18, 3.82) will be used to compute the probability that one would observe 1 or more subjects with TLTs out of the remaining 3, the average number subjects with at least one TLT, the variability around these estimates, etc. In addition, the 95% credible interval for the TLT rate will be derived from the posterior distribution. These and other characteristics of the posterior distribution and posterior predictive distribution may aid in the evaluation of TLT rates.

11.4.2. Statistical Methods for Safety Parameters

Descriptive statistics will be provided for demography, safety and disease assessments within each Arm by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

The safety profile will be based on AEs reported including TLTs (Arm 2), AEs of special interest, vital signs measurements, clinical laboratory measurements, ECG recordings, and physical examination results.

Adverse Events – All AEs will be listed and coded by the MedDRA. Subjects with at least one TLT (Arm 2) will be listed. The number and percent of subjects reporting any treatment-emergent AEs will be tabulated by system organ class and preferred term and

categorized by dose. AEs with missing date of onset will be considered treatment-emergent. AEs will be tabulated by severity, relationship to treatment, and seriousness. Tables and/or narratives of any on study death, or serious or significant AE, including early withdrawals because of AEs, will be provided should they occur.

Vital Signs – Vital signs will be listed and reviewed for each subject. Depending on the size and the scope of changes, summaries of vital signs data over time and/or changes from pre-dose value over time may be provided.

Electrocardiogram – ECG data will be listed and reviewed for each subject. Fridercia's and Bazett's correction will be used to adjust QT for RR. Summaries of ECG intervals and/or the change from baseline will be provided. Baseline ECG parameters will be based on the mean of the screening and pre-dose ECG assessments.

T-cell Phenotype and Cytokines – The results will be listed.

Clinical Laboratory Tests – Clinical chemistry, hematology, and urinalysis data will be listed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Laboratory abnormalities will be graded using NCI-CTCAE v 4.0. Each subject's maximum post-baseline grade will be computed for each laboratory parameter and referred to as their worst grade for that laboratory parameter. For each parameter shift tables from baseline to worst grade may be presented.

11.5. Statistical Methods for Antitumor Activity Endpoints

ORR is defined as the proportion of subjects with a confirmed sCR, CR, VGPR and PR using IMWG uniform response criteria for MM [Kumar, 2016]. ORR is the key clinical endpoint for assessing antitumor activity.

ORR will be estimated for each arm using two-sided 95% Wilson and exact based confidence intervals (CIs). The study is not powered to conduct statistical comparisons of the observed ORR to a historical control rate. Bayesian posterior probabilities for the ORR within each arm may be calculated with a range of assumptions that will be outlined in the RAP.

Other endpoints such as TTR, DOR, PFS and OS, will be summarized descriptively if data warrant.

Definitions:

- TTR, defined as the time from T-cell infusion to initial date of response of the subjects who achieved confirmed sCR, CR, VGPR or PR.
- DOR, defined as the time from the initial date of response of the subjects who achieved confirmed sCR, CR, VGPR or PR to the date of progressive disease or death.
- PFS, defined as the interval between the date of T-cell infusion and the earliest date of disease progression or death due to any cause.

- OS, defined as the time from T-cell infusion to death due to any cause. Subjects who are alive will be censored at the date of last contact.

Time to event endpoints will be summarized and displayed graphically using Kaplan-Meier methodology to estimate the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as the proportion of censored observations if data warrant. OS will also be assessed descriptively at fixed time points such as 1 year and 2 years using proportions and Kaplan-Meier methods if data warrant.

12. CLINICAL SUPPLIES

12.1. Packaging and Labelling

12.1.1. NY-ESO-1^{c259}T-cell Product

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

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

12.1.2. Pembrolizumab

Clinical supplies of pembrolizumab will be provided by the Sponsor as summarized in Table 16.

Table 16 Pembrolizumab Product Description

Product Name & Potency	Dosage Form
MK-3475 100 mg/4 mL	Solution for Injection

12.2. Standard Policies and Product Return

IPs must be received by a designated person at the site, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated assistants have access. IPs are to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the IPs received from the Sponsor, the amount dispensed, and the unused IPs remaining or destroyed at the conclusion of the study. The Sponsor or designee should be contacted regarding any questions concerning both IPs. At the end of the study or as dictated by protocol or process, all clinical supplies will be returned or destroyed as indicated.

All sites should contact the Sponsor or designee for specific instructions for IP returns or destruction and appropriate documentation for drug accountability.

12.3. Storage and Handling

The subject's T-cell product that is received at the site will be stored below -135°C. The cell product will be thawed and infused as specified in Section 5.3.

12.4. Product Accountability

The two IPs provided for this study are for use only as directed in the protocol. It is the Investigator/institution's responsibility to establish a system for handling both IPs as to ensure that:

- Deliveries of IPs are correctly received by a responsible person.
- Such deliveries are recorded.
- IPs are handled and stored safely and properly as stated on their respective label.
- IPs are only dispensed to study subjects in accordance with the protocol.
- Any unused NY-ESO-1^{c259}T product is returned to the Commercial Manufacturing Location (CML) and accounted for in the site records.
- Any unused pembrolizumab product is destroyed per institution practice and accounted for in the site records.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed stock. Records of usage should include the bag number (for NY-ESO-1^{c259}T) or the container number (for pembrolizumab), the identification of the person (subject ID) to whom the IP(s) were dispensed and the quantity and date of dispensing. This record is in addition to any IP information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. All unused IP should be returned or destroyed once appropriate IP accountability procedures are performed by the Monitor or clinical research associate (CRA). Refer to SPM for further details.

13. DATA HANDLING AND RECORD KEEPING

13.1. Data Management

An EDC system will be used to collect data pertaining to this trial. Trial data will be captured through an eCRF. Within the EDC system the eCRF data will be entered by the site staff and all source document verification and data cleaning will be performed by the Sponsor or designee (e.g., contract research organization [CRO]).

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

The EDC system is a validated software program that has been designed to comply with 21 CFR Part 11 requirements. All users will access the system via unique user name and password. A full audit history of all actions performed within the system is maintained. User accounts ensure that each user can only perform the tasks applicable to their role and only have access to the data applicable to their role. Standard coding dictionaries, WHO Drug and MedDRA, will be used to code medications and AEs.

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

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

13.2. Case Report Forms

For each subject enrolled, an eCRF must be completed and signed by the principal Investigator or authorized delegate. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment limiting AE, thorough efforts should be made to clearly document the outcome.

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

13.3. Site Documentation and Source Data

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

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

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

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

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

13.4. Data Retention and Availability

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

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

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

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

14. STUDY MONITORING

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

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

It will be the monitors' responsibility to inspect the eCRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have direct access to subject source documents to verify the entries on the eCRF. The Investigator (or designee) agrees to cooperate with the monitor to ensure any discrepancies detected are resolved.

14.1. Audits and Inspections

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

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

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

Regulatory agencies may also inspect investigative sites during or after the study. The Investigator (or designee) should contact the Sponsor immediately if this occurs, and provide copies of correspondence relating to requests for an inspection of the site facilities.

15. REGULATORY AND ETHICAL CONSIDERATIONS

15.1. Competent Authority Submissions

GSK or its authorized representatives will be responsible for ensuring that appropriate competent authority approvals are obtained according to local country requirements. Competent authority approval (or notification as applicable) will be obtained before initiation of the study.

15.2. Independent Ethics Committees

The final study protocol and subject informed consent documentation will be approved by the IRB/IEC and any other site level committee deemed appropriate by the Institution. Approval from each applicable committee will be received in writing before initiation of the study.

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

15.3. Local Regulations/Declaration of Helsinki

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

15.4. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study related procedures being performed. All consent documentation must be in accordance with applicable regulations and ICH GCP. Documentation must include the dated signature of both the subject (or the subject's parents or legally authorized representative as applicable) and the person conducting the consent discussion. If the subject is illiterate, an impartial witness should be present during the consent discussion, and the consent signed and dated by the witness, the subject, and the person conducting the consent discussion. The consent form should be translated and communicated to the subject in a language that is understandable to the subject. Certified translations of the informed consent documentation will be provided as applicable.

A copy of the signed and dated informed consent should be provided to the subject before participation in the study.

Tests performed as standard of care prior to documentation of consent may be used for screening results as appropriate.

15.5. Confidentiality

The confidentiality of records that may identify subjects will be protected in accordance with applicable laws, regulation and guidelines.

The Investigator must ensure that each subject's anonymity is maintained and protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, subjects must not be identified by their names, but by a unique identification code allocated to them to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study.

The Investigator will keep a subject enrollment log showing subject unique identification codes, names and addresses in the ISF.

The Sponsor and/or its representatives accessing subject records and data at site will take all reasonable precautions to maintain subject confidentiality.

15.6. Protocol Adherence

The Investigator must sign the protocol to confirm acceptance and willingness to comply with the study protocol.

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

15.7. Study Suspension, Study Termination and Study Completion

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

If the Investigator stops/terminates the study at their site, the Sponsor must be notified. The Sponsor will ensure Regulatory Agencies and IRBs/IECs are notified as appropriate.

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

15.8. Public Posting of Study Information

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

15.9. Clinical Study Report

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

15.10. Publication Policy

The Investigator may not submit the results of the study for publication or present the results of the study without the prior written agreement of the Sponsor in accordance with the Clinical Trial Agreement. The results of this study will be published as a whole once all subjects have completed the study and the study results have been analyzed. Interim publications of data from the study may be made if mutually agreed between the Sponsor and the Investigators. Agreement will not be provided by the Sponsor where in the Sponsor's view interim publications would introduce bias or lead to any misrepresentation or inaccuracies in data.

Authorship will be determined in conformance with the International Committee of Medical Journal Editors (ICMJE) guidelines and/or publication guidelines if applicable.

16. APPENDICES

16.1. List of Abbreviations and Definitions of Terms

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

Abbreviations and Specialist Terms

ACT	Adoptive cell therapy
ADC	Antibody-drug conjugate
AE	Adverse event
aGVHD	Autologous graft versus host disease
ALK	Anaplastic lymphoma kinase
allo-SCT	Allogeneic stem cell transplant
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BBB	Bundle branch block
BCMA	B cell maturation antigen
BM	Bone marrow
BP	Blood pressure
CAR	Chimeric antigen receptor
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
cfDNA	Cell-free DNA
CFR	Code of Federal Regulations

CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMLCMV	Commercial Manufacturing LocationCytomegalovirus
CNS	Central nervous system
CR	Complete response
CRA	Clinical research associate
CRAB	Calcium elevation, renal insufficiency, anemia, and bone abnormalities
CRES	Cell-related encephalopathy syndrome
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CTA	Cancer testes antigen
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CV	Cardiovascular
DC	Discontinuation
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
DNA	Deoxyribonucleic acid
DOR	Duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram

ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMG	Electromyography
ES	Encephalopathy syndrome
ESI	Events of Special Interest
EU	European Union
FCM	Flow cytometry
FDA	Food and Drug Administration
FLC	Free light chain
FSH	Follicle-stimulating hormone
GBS	Guillain-Barré Syndrome
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GGTP	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GLP	Good laboratory practice
GMP	Good manufacturing practice
GVHD	Graft-versus-host disease

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematopoietic cell transplantation
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormonal replacement therapy
HTLV	Human T-lymphotropic virus
IB	Investigator's Brochure
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug application
INDSR	Investigational new drug safety reports
INL	Investigator Notification Letter
INR	International normalised ratio
IP	Investigational Product

irAE	Immune-related adverse event
IRB	Institutional Review Board
ISF	Investigator Site File
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
ITT	Intent-to-treat population
IV	Intravenous
LDH	Lactic acid dehydrogenase
LTFU	Long-term follow-up
LTR	Long terminal repeat
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	Modified intent-to-treat population
MM	Multiple myeloma
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition scan
NCI	National Cancer Institute
nCR	Near complete response

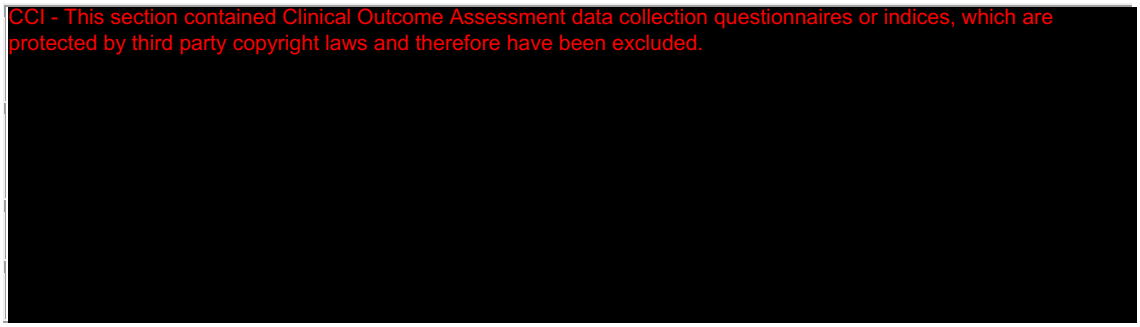
NCI	National Cancer Institute
NGS	Next-Gen Sequencing
NIH	National Institutes of Health
NK	Natural killer
NR	Not reached
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically-based pharmacokinetic
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q2W	Every 2 weeks

Q3W	Every 3 weeks
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAC	Recombinant DNA Advisory Committee
RAP	Reporting and Analysis Plan
RC	Research Committee
RCL	Replication competent lentivirus
RCR	Replication competent retrovirus
RSD	Reference Safety Dataset
RN	Registered nurse
RNA	Ribonucleic acid
RRMM	Relapsed and refractory multiple myeloma
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SC	Subcutaneous
sCR	Stringent complete response
Scrn	Screening
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIN	Self-inactivating
SMM	Smoldering multiple myeloma
SOP	Standard operating procedure

SPM	Study procedures manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
TCR	T-cell receptors
TILs	Tumor-infiltrating lymphocytes
TLT	Treatment-limiting toxicities
TSH	Thyroid stimulating hormone
TTP	Time to progression
Tx	Treatment
ULN	Upper limits of normal
USPI	United States Prescribing Information
VGPR	Very good partial response
VSV-G	Vesicular stomatitis virus envelope glycoprotein
V-type	Variable type
WBC	White blood cell
WOCBP	Women of childbearing potential
WPRE	Woodchuck hepatitis post-transcriptional regulatory element

16.2. ECOG Performance Status

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



[Oken, 1982]

16.3. Laboratory Tests and ECG

Hematology, Chemistry and Urinalysis Variables	
Clinical Chemistry:	Calcium Phosphorus Magnesium Albumin Bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Lactate dehydrogenaase Sodium Potassium Bicarbonate Creatinine* Chloride Glucose BUN or Urea * In subjects ≥65 years add GFR
Hematology:	Red cell count Hemoglobin Hematocrit Mean cell volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelet count White blood cell count & differential count (percent & absolute)
Coagulation Screen:	Prothrombin time *or* International Normalized Ratio Activated partial thromboplastin time

Hematology, Chemistry and Urinalysis Variables	
Microbiology:	**Infectious disease screen**: HIV 1+2 antibody Hepatitis B surface antigen Hepatitis B core antibody – if positive, test for HBV DNA Hepatitis C antibody – if positive, test for HCV RNA HTLV 1+2 IgG CMV IgG EBV (EBNA) Syphilis (RPR) **Viral reactivation**: CMV DNA PCR – peripheral blood for detection of reactivation.
Pregnancy Test:	Serum beta-HCG or Urine test
Thyroid Function Tests:	TSH
Other Tests:	Uric Acid C-reactive protein
ECG Parameters:	Heart Rate Heart Rhythm PR Interval RR Interval QRS Interval QTc Interval (Fridericia's or Bazett's correction)
Urinalysis:	Glucose Ketones Specific gravity Protein Blood Microscopy Bilirubin pH

16.4. International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features and myeloma-defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177µmol/L (>2 mg/dL)
  - Anemia: hemoglobin value of >20 g/L below the lowest limit of normal, or a hemoglobin value <100 g/L
  - Bone lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT. If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

- Any one or more of the following biomarkers of malignancy (MDEs):
  - 60% or greater clonal plasma cells on bone marrow examination
  - Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100 mg/L (a patient's "involved" free light chain—either kappa or lambda—is the one that is above the normal reference range; the "uninvolved" free light chain is the one that is typically in, or below, the normal range)
  - More than one focal lesion on MRI that is at least 5 mm or greater in size.

Abbreviations: CR, complete response; FLC, free light chain; M, monoclonal; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

16.5. Response Rates in Subjects with Relapsed and Refractory Multiple Myeloma

The response rates in subjects with RRMM are shown in the table below. In subjects who have received a median of 5 prior therapies, the response rates range from 23.7% with single agent carfilzomib [Siegel, 2012] to 33% with pomalidomide/dexamethasone [Richardson, 2014]. Higher response rates in excess of 50% are observed in subjects who have received a median of 2 prior therapies [San-Miguel, 2014; Garderet, 2012; Stadtmauer, 2013; Dimopoulos, 2013; Lonial, 2015; Stewart, 2015]. These subjects appear to have less refractory disease. The study population based on the eligibility criteria in our study will be a relapsed and refractory population and it is estimated that the historic response rate would be ~25%. A response rate of 45% with a median DOR in excess of 6 would be of clinical significance.

Author/Study/Subjects	Regimen	ORR	Median PFS/OS
Richardson, 2014 Phase 2 (N=221) Median 5 prior therapies	Pom/Dex vs. Pom	33% vs. 18%	PFS: 4.2 m vs. 2.7 m OS: 16.5 m vs. 13.6 m
San-Miguel, 2014 Phase 3 (N=387)	Pano/Vel/Dex vs. Vel/Dex	60.7% vs. 54.6%	PFS: 11.99 m vs. 8.08 m OS: 33.64 m vs. 30.39 m
Siegel, 2012 Phase 2 (N=266) Median of 5 lines of therapy	Single agent carfilzomib	23.7%	Median duration of response: 7.8 m OS: 15.6 m
Garderet, 2012 Phase 3 (N=269) MM patients progressing or relapsing after autologous HCT	Vel/Thal/Dex vs. Thal/Dex	88% vs. 72%	Median duration of response: 17.9 vs 13.4 m 2-year OS: 71% vs. 65%
Stadtmauer, 2013 Phase 2 (N=72) Median 6 prior regimens	Car/Pom/Dex	64%	PFS:12 m OS: 16.3 m
Dimopoulos, 2013 Phase 3 (N=637) Median 2 prior regimens	Vorinostat + Vel vs. Vel	56.2% vs. 40.6%	PFS: 7.63 m vs. 6.83 m
Lonial, 2015 Phase 3 (N=646) Median 2 prior regimens	Elotuzumab + Rev/Dex vs. Rev/Dex	79% vs. 66%	1-year PFS: 68% vs. 57% PFS: 19.4 m vs. 14.9 m
Stewart, 2015 Phase 3 (N=792) Median 2 prior regimens	Car/Rev/Dex (KRD) vs. Rev/Dex	87.1% vs. 66.7%	PFS: 26.3 m vs. 17.6 m 24-m OS: 73.3% vs. 65%
FDA label Study 1 Phase 1 (N=106) At least 3 prior regimens Study 2 (N=42) Median 4 prior regimens	Daratumumab	Study 1: 29% Study 2: 36%	

Abbreviations: car, carfilzomib; dex, dexamethasone; pano, panobinostat; PFS, progression-free survival; pom, pomalidomide; ORR, overall response rate; OS, overall survival; rev, lenalidomide; thal, thalidomide; vel, bortezomib

16.6. Liver Safety Required Actions and Follow up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE**[2]** • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or	• Viral hepatitis serology[4] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN, obtain NY-ESO peripheral blood cell level assessment • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form

return to within baseline (see **MONITORING** below) • **Do not restart** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Section 4.8) **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that 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, 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)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal F, 2005].

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

17. LIST OF REFERENCES

American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019.

Andrade VCC, Vettore AL, Felix RS, Almeida MSS, Carvalho F, Oliveira JSR, et al. Prognostic impact of cancer/testis antigen expression in advanced stage multiple myeloma patients. *Cancer Immun*. 2008;8:2. URL: http://archive.cancerimmunity.org/v8p2/071018.pdf.

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with pembrolizumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319.

Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med*. 1996;335(2):91-97.

Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1782-1791.

Baccala R, Gonzalez-Quintial R, Dummer W, Theofilopoulos AN. Tumor immunity via homeostatic T-cell proliferation: mechanistic aspects and clinical perspectives. *Springer Semin Immunopathol*. 2005;27(1):75-85.

Badros AZ, Kocoglu MH, Ma N, et al. A Phase II study of anti PD-1 antibody pembrolizumab, pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). ASH 2015 Annual Meeting Abstract 506 (Oral Presentation).

Barrett J, Blazar BR. Genetic trickery--escape of leukemia from immune attack. *N Engl J Med*. 2009;361(5):524-525.

Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2011;29(31):4189-4198.

Becker N. Epidemiology of multiple myeloma. *Recent Results Cancer Res*. 2011;183:25-35.

Benson DM, Bakan CE, Mishra A, et al. The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. *Blood*. 2010;116(13):2286-2294.

Besser MJ, Shapira-Frommer R, Treves AJ et al. Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. *Clin Cancer Res*. 2010;16(9):2646-2655.

Cattoglio C, Maruggi G, Bartholomae C, et al. High-definition mapping of retroviral integration sites defines the fate of allogeneic T cells after donor lymphocyte infusion. *PLoS ONE*. 2010;5(12):e15688. doi: 10.1371/journal.pone.0015688.

Chemnitz, JM, Parry, RV, Nichols, KE, et al. SHP-1 and SHP-2 Associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol*. 2004, 173(2): 945–954.

Cheng X, Veverka V, Radhakrishnan A, et al. Structure and interactions of the human programmed cell death 1 receptor. *J Biol Chem*. 2013;288(17):11771-11785.

Cheson BD. Infectious and immunosuppressive complications of purine analog therapy. [Review]. *J Clin Oncol*. 1995;13(9):2431-2448.

Chong H, Starkey W, Vile RG. A replication-competent retrovirus arising from a split-function packaging cell line was generated by recombination events between the vector, one of the packaging constructs, and endogenous retroviral sequences. *J Virol*. 1998;72(4):2663-2670.

Condomines M, Hose D, Raynaud P, Hundemer M, De Vos J, Baudard M, et al. Cancer/testis genes in multiple myeloma: expression patterns and prognosis value determined by microarray analysis. *J Immunol*. 2007;178(5):3307–15.

Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T-cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med*. 2014;6(224):224ra25. doi: 10.1126/scitranslmed.3008226.

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

Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicenter, randomized, double-blind study. *Lancet Oncol*. 2013;14(11):1129-1140.

Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357(21):2123–2132.

Disis, ML. Immune Regulation of Cancer. *J Clin Oncol*. 2010; 28(29):4531-4538.

Donahue RE, Kessler SW, Bodine D, et al. Helper virus induced T-cell lymphoma in nonhuman primates after retroviral mediated gene transfer. *J Exp Med*. 1992;176(4):1125-1135.

Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol*. 2005;23(10):2346-57.

Dull T, Zufferey R, Kelly M, et al. A Third-Generation Lentivirus Vector with a Conditional Packaging System. *J Virol*. 1998;72(11):8463-8471.

Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1476-1473.

European Medicines Agency (EMA). EMEA/CHMP/GTWP/60436/2007. CHMP Guideline on Follow-Up of Patients administered with Gene Therapy. 2009.

Evans JP. Fertilin beta and other ADAMs as integrin ligands: insights into cell adhesion and fertilization. *Bioessays*. 2001;23(7):628–639.

Fidler C, Klumpp T, Mangan K, et al. Spontaneous graft versus host disease occurring in a patient with multiple myeloma after autologous stem cell transplant. *Am J Hematol*. 2012;87(2):219-221.

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

Food and Drug Administration (FDA). Guidance for industry: Supplemental guidance on testing for replication competent retrovirus in retroviral vector based gene therapy products and during follow-up of patients in clinical trials using retroviral vectors. 2006.

Food and Drug Administration (FDA). Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products. January 2020.

FDA Nov 2010: Briefing Document — Testing for Replication Competent Retrovirus (RCR)/Lentivirus (RCL) in Retroviral and Lentiviral Vector Based Gene Therapy Products — Revisiting Current FDA Recommendations.

Francisco, LM, Sage, PT, and Sharpe, AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Reviews*. 2010; 0105-2896.

Garderet L, Iacobelli S, Moreau P, et al. Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2012;30(20):2475-2482.

Garfall AL, Kalos M, Furth EE, et al. Autologous aGVHD Associated with Infusion of T-Cells with Engineered Specificity for NY-ESO-1 and LAGE-1 Following High-Dose Melphalan and ASCT in Patients with Multiple Myeloma. *Biol Blood Marrow Transplant*. 2013;19:S134.

Garrett E, Miller AR, Goldman JM, Apperley JF, Melo JV. Characterization of recombination events leading to the production of an ecotropic replication-competent retrovirus in a GP+envAM12-derived producer cell line. *Virol*. 2000;266(1):170-179. doi: 10.1006/viro.1999.0052.

Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18(4):295-304.

Gorgun G, Samur MK, Cowens KB, et al. Lenalidomide enhances immune checkpoint blockade induced immune response in multiple myeloma. *Clin Cancer Res*. 2015;21(20):4607-4618.

Greenwald, RJ, Freeman, GJ, and Sharpe, AH. The B7 Family Revisited. *Annu Rev Immunol*. 2005; 23:515–48.

Hacein-Bey-Abina S, Pai S, Gaspar HB, et al. A modified γ-retrovirus vector for X-Linked severe combined immunodeficiency. *N Engl J Med*. 2014;371(15):1407-1417.

Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science*. 2003;302(5644):415-419.

Hallett WH, Jing W, Drobyski WR, Johnson BD. Immunosuppressive effects of multiple myeloma are overcome by PD-L1 blockade. *Biol Blood Marrow Transplant*. 2011;17(8):1133-1145.

Huang X, Venet F, Wang YL, et al. PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. *Proc Natl Acad Sci U S A*. 2009;106(15):6303-6308.

Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N Engl J Med.* 2008;358(25):2698-703.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

GSK Document Number 2018N369930_03, Investigator Brochure for GSK3377794 (NY-ESO-1^{c259}T): Version 11. 20 Nov 2019.

Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci USA*. 2002;99(19):12293-12297.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Johnson LA, Morgan RA, Dudley ME, et al. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. *Blood*. 2009;114(3):535-546.

Kalos M, June CH. Adoptive T-cell transfer for cancer immunotherapy in the era of synthetic biology. *Immunity*. 2013;39(1):49-60. doi: 10.1016/j.immuni.2013.07.002.

Karim R, Jordanova ES, Piersma SJ, et al. Tumor-expressed B7-H1 and B7-DC in relation to PD-1+ T-cell infiltration and survival of patients with cervical carcinoma. *Clin Cancer Res*. 2009;15(20):6341-6347.

Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2015;162(3):205-213.

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677-704.

Keytruda USPI. http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. 2020. Accessed 17 February, 2020.

Klebanoff CA, Rosenberg SA, Restifo NP. Prospects for gene-engineered T-cell immunotherapy for solid cancers. *Nat Med*. 2016;22(1):26-36.

Kline J, Subbiah S, Lazarus HM, van Besien K. Autologous graft-versus-host disease: harnessing anti-tumor immunity through impaired self-tolerance. *Bone Marrow Transplant*. 2008;41(6):505-513.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet*. 2016;17:e328-e346.

Kuranda K, Berthon C, Dupont C, et al. A subpopulation of malignant CD34+CD138+B7-H1+ plasma cells is present in multiple myeloma patients. *Exp Hematol*. 2010;38(2):124-131.

Lazar-Molnar E, Yan Q, Cao E, Ramaqopal U, Nathenson SG, Almo SC. Crystal structure of the complex between programmed death-1 (PD-1) and its ligand PD-L2. *Proc Natl Acad Sci U S A*. 2008;105(30):10483-10488.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates

Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-638.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195. doi: 10.1182/blood-2014-05-552729.

Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. *Clin Trials.* 2008;5(2):93-106.

Lesokhin AM, Ansell SM, Armand P, et al. Preliminary results of a Phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. *Blood*. 2014;124(21):291-291.

Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2009;150:604-612.

Lin DY, Tanaka Y, Iwasaki M, et al. The PD-1/PD-L1 complex resembles the antigen-binding Fv domains of antibodies and T cell receptors. *Proc Natl Acad Sci U S A*. 2008;105(8):3011-3016.

Liu J, Hamrouni A, Wolowiec D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. *Blood*. 2007;110(1):296-304.

Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373(13):1207-1219.

Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373(7):621-631.

Manilla P, Rebello T, Afable C, et al. Regulatory considerations for novel gene therapy products: a Review of the process leading to the first clinical lentiviral vector. *Human Gene Ther*. 2005;16(1):17–25.

Marincola FM, Jaffee EM, Hicklin DJ, Ferrone S. Escape of human solid tumors from T cell recognition: molecular mechanisms and functional significance. *Adv Immunol*. 2000;74:181-273.

Maruggi G, Porcellini S, Facchini G, et al. Transcriptional enhancers induce insertional gene deregulation independently from the vector type and design. *Mol Ther*. 2009;17(5):851-856.

Mateos M-V, Blacklock H, Schjesvold MD, et al. Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomized, open-label, phase 3 trial. The Lancet 2019;6(9):e459-e469.

Mateos M-V, Orlowski RZ, DiCapua DS, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): Final efficacy and safety analysis. *J Clin Oncol* 34, 2016 (suppl; abstr 8010).

Matsui W, Wang Q, Barber JP, et al. Clonogenic multiple myeloma progenitors, stem cell properties, and drug resistance. *Cancer Res*. 2008;68(1):190–197.

Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J*. 2014;20(2):119-122. doi: 10.1097/PPO.0000000000000035.

Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. *Blood*. 2014;123(17):2625-2635. doi: 10.1182/blood-2013-11-492231.

McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1770-1781.

Merchant MS, D'Angelo SP, Zhang H, et al. Genetically engineered NY-ESO-1-specific T cells in HLA-A2+ patients with synovial sarcoma. *Cancer Res*. 2015;75(15 Supplement):4707-4707.

Miller AD. Retrovirus packaging cells. *Hum Gene Ther*. 1990;1(1):5-14. doi: 10.1089/hum.1990.1.1-5.

Modlich U, Navarro S, Zychlinski D, et al. Insertional transformation of hematopoietic cells by self-inactivating lentiviral and gammaretroviral vectors. *Mol Ther*. 2009;17(11):1919-1928. doi: 10.1038/mt.2009.179.

Montini E, Cesana D, Schmidt M, et al. The genotoxic potential of retroviral vectors is strongly modulated by vector design and integration site selection in a mouse model of HSC gene therapy. *J Clin Invest*. 2009;119(4):964-975.

Montini E, Cesana D, Schmidt M, et al. (2006). Hematopoietic stem cell gene transfer in a tumor-prone mouse model uncovers low genotoxicity of lentiviral vector integration. *Nat Biotechnol*. 2006;24(6):687-696.

Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. *Mol Ther*. 2010;18(4):843-851. doi: 10.1038/mt.2010.24.

Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47-62.Newrzela S, Cornils K, Li Z, et al. Resistance of mature T cells to oncogene transformation. *Blood*. 2008;112(6):2278-2286. doi: 10.1182/blood-2007-12-128751.

Nishimura H, Agata Y, Kawasaki A, et al. Developmentally regulated expression of the PD-1 protein on the surface of double-negative (CD4-CD8-) thymocytes. *Int Immunol*. 1996;8(5):773-780.

Okazaki T, Maeda A, Nishimura H, et al. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci* USA. 2001;98(24):13866-71.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.

Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clin Cancer Res*. 2013;19(19):5300-5309.

Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371(10):895-905.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009;54:84-90.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264.

Parry, RV, Chemnitz, JM, Frauwirth, KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Molec Cell Biol*. 2005;0270-7306.

Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A. Programmed death-1 pathway in cancer and autoimmunity. *Clin Immunol*. 2014;153(1):145-152.

Pembrolizumab (Keytruda) Investigator's Brochure Edition Number 17. Release Date 26 July 2019. Merck Sharp & Dohme Corp a subsidiary of Merck & Co., NJ, USA

Pena-Cruz V, McDonough SM, Diaz-Griffero F, Crum CP, Carrasco RD, Freeman GJ. PD-1 on immature and PD-1 ligands on migratory human Langerhans cells regulate antigen-presenting cell activity. *J Invest Dermatol*. 2010;130(9):2222-2230.

Pinthus JH, Waks T, Malina V, et al. Adoptive immunotherapy of prostate cancer bone lesions using redirected effector lymphocytes. *J Clin Invest*. 2004;114(12):1774-1781.

Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia. *New Engl J Med*. 2011;365(8):725-733.

Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *New Engl J Med*. 2019 ;380(18) :1726-1737.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.

Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*. 2005;106(13):4050–4053.

Rapoport AP, Stadtmauer EA, Binder-Scholl GK, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. *Nat Med*. 2015;21(8):914-921. doi: 10.1038/nm.3910.

Rapoport, AP, Stadtmauer EA, Aqui N, et al. Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T cell transfer. *Nat Med*. 2005;11(11):1230-1237. doi: 10.1038/nm1310.

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

Rapoport AP, Stadtmauer EA, Chagin K, et al. Phase I/IIa study of genetically engineered NY-ESO-1 SPEAR T-cells administered following autologous stem cell transplant in HLA-A*02+ patients with advanced multiple myeloma: long-term follow-up. ASH Annual Meeting in Atlanta 9-12 Dec 2017.

Revlimid USPI. http://www.revlimid.com/wp-content/uploads/full-prescribing-information.pdf revised 02/2015.

Richardson P, Barlogie B, Berenson JR, et al. Prognostic factors associated with response in patients with relapsed and refractory multiple myeloma (MM) treated with bortezomib. *Proc Am Soc Clin Oncol*. 2003;22:abstract 2337, page 581.

Richardson PG, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. *Blood*. 2016;127(6):713-721.

Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood*. 2014;123(12):1826-1832.

Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352(24):2487-2498.

Riley, JL, PD-1 signaling in primary T cells. *Immunol Rev*. 2009;0105-2896.

Robbins PF, Morgan RA, Feldman SA, et al. Tumor Regression in Patients With Metastatic Synovial Cell Sarcoma and Melanoma Using Genetically Engineered Lymphocytes Reactive With NY-ESO-1. *J Clin Oncol*. 2011;29(7):917-924. doi: 10.1200/jco.2010.32.2537.

Robbins, PF, Kassim SH, Tran TL, et al. A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1–Reactive T cell Receptor: Long-term Follow-up and Correlates with Response. *Clin Cancer Res*. 2015;21(5):1019-1027.

Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. [Review]. *Nat Rev Cancer*. 2008;8(4):299-308. doi: 10.1038/nrc2355.

Rosenblatt J, Glotzbecker B, Mills H, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. *J Immunother*. 2011;34(5):409-418.

Sanmamed MF, Chen L. Inducible expression of B7-H1 (PD-L1) and its selective role in tumor site immune modulation. *Cancer J*. 2014;20(4):256-261.

San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicenter, randomized, double-blind phase 3 trial. *Lancet Oncol*. 2014;15(11):1195-1206.

San Miguel J, Mateos M-V, Shah JJ, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): Keynote-023. *Blood*. 2015;126(23):505-505.

Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett*. 2004;574(1-3):37-41.

Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood*. 2012;120(14):2817-2825.

Sponaas A-M, Moharrami NN, Feyzi E, et al. PDL1 Expression on Plasma and Dendritic Cells in Myeloma Bone Marrow Suggests Benefit of Targeted anti PD1-PDL1 Therapy. *PLoS ONE* 2015;10(10):e0139867. doi:10.1371/journal.pone.0139867

Stadtmauer EA, Abonour R, Cohen AD, et al. Phase I/II dose expansion of a multi-center trial of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) in patients with relapsed/refractory multiple myeloma. *Blood*. 2013;122(21):690.

Stadtmauer EA, Faitg TH, Lowther DE, et al. Long-term safety and activity of NY-ESO-1 SPEAR T cells after autologous stem cell transplant for myeloma. *Blood Adv*. 2019;3(13):2022-2034.

Stein S, Ott MG, Schultze-Strasser S, et al. Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease. *Nat Med*. 2010;16(2):198–204.

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-152.

Taube JM, Anders RA, Young GD, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med*. 2012;4(127):127ra37.

Timmers M, Roex G, Wang Y, et al. Chimeric antigen receptor-modified T cell therapy in multiple myeloma: beyond B cell maturation antigen. *Frontiers in Immun*. 2019;10;1613. doi: 10.3389/fimmu.2019.01613.

Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol*. 2012;24(2):207-212.

Trudel S, Lendvai N, Popat R, et al. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma : an update on safety and efficacy from dose expansion phase I study. Blood Cancer J. 2019 ; 9,37. doi:10.1038/s41408-019-0196-6.

Turtle CJ, Hanafi L-A, Berger C, et al. CD19 CAR–T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *J Clin Invest*. 2016;126(6): 2123–2138.

Usmani SZ, Schjesvold F, Oriol A, et al. Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naïve multiple myeloma (KEYNOTE-185): a randomized, open-label, phase 3 trial. The Lancet. 2019;6(9):e448-e458.

van Baren N, Brasseur F, Godelaine D, Hames G, Ferrant A, Lehmann F, et al. Genes encoding tumor-specific antigens are expressed in human myeloma cells. *Blood*. 1999;94(4):1156–1164.

van Duin M, Broyl A, de Knegt Y, et al. Cancer testis antigens in newly diagnosed and relapse multiple myeloma: prognostic markers and potential targets for immunotherapy. *Haematologica*. 2011;96(11):1662–1669.

van Rhee F, Szmania SM, Zhan F, et al. NY-ESO-1 is highly expressed in poor-prognosis multiple myeloma and induces spontaneous humoral and cellular immune responses. *Blood*. 2005;105(10):3939-3944.

Vij R, Wang M, Kaufman JL, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. *Blood*. 2012;119(24):5661-5670.

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

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

Wallen H, Thompson JA, Reilly JZ, Rodmyre RM, Cao J, Yee C. Fludarabine modulates immune response and extends in vivo survival of adoptively transferred CD8 T cells in patients with metastatic melanoma. *PLoS ONE*. 2009;4(3):e4749.

Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357(21):2133–2142.

Willison HJ, Jacobs BC, van Doom PA. Guillain-Barre Syndrome. *Lancet*. 2016;388(10045):717-727.

Wolf AM, Wolf D, Steurer M, Gastl G, Gunsilius E, Grubeck-Loebenstein B. Increase of regulatory T cells in the peripheral blood of cancer patients. *Clin Cancer Res*. 2003;9(2):606-612.

Yao S, Chen L. PD-1 as an immune modulatory receptor. *Cancer J*. 2014;20(4):262-264.

Yousef S, Marvin J, Steinbach M, et al. Immunomodulatory molecule PD-L1 is expressed on malignant plasma cells and myeloma-propagating pre-plasma cells in the bone marrow of multiple myeloma patients. *Blood Cancer J* 2015;5, e285.

Zhang X, Schwartz JC, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity*. 2004;20(3):337-347.

Zonder JA, Crowley J, Hussein MA, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed

multiple myeloma (NDMM): results of the randomized, double-blinded, placebo-controlled SWOG trial S0232. *Blood*. 2007;110:A77.

18. CHANGE HISTORY

Protocol v2.0 (Amendment 1)

1- Integration of the sequential screening tests for HLA-genotyping and NY-ESO-1/LAGE-1a antigen expression level determination by RT-PCR into the investigational protocol
Relevant sections amended: Study design: • Section 3.1; Figure 1; Section 3.2.1 Procedures: • Sections 7; 7.1; 7.1.1; 7.1.2; 7.1.3; 7.1.4; 7.2; 7.3; 7.5.3
2- Update to Pembrolizumab background
Relevant section amended: • Section 1.5.1
3- Miscellaneous minor corrections/clarifications
Relevant section amended: • Section 3.6.2- Risk assessment : ▪ Clarification that enrolment will not be staggered but rather paused after first 3 subjects randomized on pembrolizumab to just match with all the other sections of the protocol. • Section 7.3- Schedule of procedures and footnotes: ▪ Clarifying that 'virology' should actually be 'infectious disease screen' ▪ Clarifying that 'Vector Copies (Persistence)' and 'VSV-G DNA (RCL)' are Central Labs. ▪ Correcting that Q12wks schedule from Week 24 falls on Week 48, not Week 52 as initially indicated • Section 7.5.2- Cytokine and soluble factor analysis: ▪ updated with new standard wording • Section 7.5.4- NY-ESO-1^{c259} T-Cell Persistence ▪ updated with new standard wording • Section 16.3- Laboratory Test and ECG ▪ Clarified wording for microbiology tests to match with Section 7.3

Protocol v3.0 (Amendment 2)

Primary Reason for Amendment

Protocol Amendment No. 01, dated 13 March 2017 is replaced by Protocol Amendment No. 02.

Subsequent to the licensing of Adaptimmune product NY-ESO by GSK, the purpose of this protocol amendment is to:

- Delete or replace references to Adaptimmune or its staff with that of GlaxoSmithKline (GSK) and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with GSK processes and procedures;
- Update of lymphodepletion regimen throughout.

Section of Amendment No. 2.0	**Change**
Throughout the document	• GSK study numbers added to former Adaptimmune study numbers • Adaptimmune replaced by GSK / "the Sponsor" where appropriate • "Adaptimmune's Safety Review Team and Safety Governance Board" replaced with "the Sponsor" where appropriate. • Update of lymphodepleting regimen
Objectives	Primary, secondary and exploratory objectives updated.
Section 1.2 Adoptive Immunotherapy with NY-ESO-1^{c259} Specific T Cells	Number of subjects treated with study drug to date updated.
Section 1.4 NY-ESO-1^{c259} T in Multiple Myeloma	Text updated with currently available information.
Section 1.5.1 Pembrolizumab Pharmaceutical and Therapeutic Background	Text updated with currently available information.
Section 3.1 Overall Study Design	Study design amended to update screening requirements, and definition of interventional phase completion, and to describe follow-up of subjects.
Section 3.2.6.1 Rationale for Pembrolizumab Dose	Rationale for pembrolizumab dose updated.

Section of Amendment No. 2.0	**Change**
Section 3.3 Assessment of Safety and TLT	Change Safety Review Committee (SRC) to Safety Review Team (SRT)
Section 3.3.4 Frequency of SRT Meetings	Set timing of SRT meetings removed. Timing will be specified in the SRT charter.
Section 3.3.5.2 TLT Definition	Minor revision of definition of toxicities not considered TLTs.
Section 3.6.2 Risk Assessment	Information on known safety profile updated.
Section 4.2.1 Inclusion Criteria	Minor revision to contraceptive requirements.
Section 4.2.2, Exclusion Criteria	Exclusion of subjects with active liver or biliary disease added, exclusion of subjects with CNS metastases added, and QTc criteria and details of hepatitis B and C tests amended.
Section 4.3 Completion of the Treatment Phase	Definition of completion of the treatment phase amended.
Section 4.4 Condition for Transfer to the LFTU Protocol – Study Completion	Definition of study completion and conditions for transfer to LFTU protocol updated.
Section 4.5 Study Withdrawal	Clarification of Investigator or designee on regaining contact with subjects to avoid loss of follow-up. Text regarding subject voluntarily withdrawing from treatment due to toxicity to be recorded as an AE, has been removed.
Section 4.6, Subject Withdrawal	Details of follow-up attempts amended, and information with regards to subjects who voluntarily discontinued added.
Section 4.7 Considerations for Temporary Suspension of Enrollment	Updated to accommodate GSK common practice.
Section 4.8 Liver Chemistry Stopping Criteria	Updated to include liver chemistry stopping and increased monitoring criteria.
Section 4.9 QTc Stopping Criteria	Updated to include QTc stopping criteria.
Section 5.2 Lymphodepleting Chemotherapy	Lymphodepleting chemotherapy regimen for the study updated.
Section 5.2.3 Cell Infusion	Details of cell infusion revised.

Section of Amendment No. 2.0	**Change**
Section 5.4.1 Schedule Modification Guidelines for Pembrolizumab (Arm 2)	Schedule modification guidelines for pembrolizumab (Arm 2) revised and details of irAEs added. Removal of AST, ALT, or increased bilirubin as replaced with liver chemistry stopping criteria.
Section 6.1 Prohibited concomitant medication and treatment	Minor revision to note on subjects receiving radiation therapy.
Section 6.3 Contraception	New contraceptive requirements added.
Section 6.3.4 Use in Pregnancy	Clarification of pregnancy complication or elective termination of pregnancy to be reported as AE or SAE.
Section 7.1.4 Companion Diagnostic Test	Clarification of text to allow for flexibility in methodology for assays.
Section 7.2 Screen Failures	Updated to include SAEs.
Section 7.3 Schedule of Procedures	Minor revisions to schedule of procedures to reflect changes throughout the protocol, including addition of Brain MRI and CARTOX 10. Schedule of procedures for LFTU protocol updated.
Section 7.4.5 Laboratory Assessments	Clarification of pregnancy test assessments.
Section 7.4.6 Cardiac Assessments	Requirement for inpatient telemetry monitoring for subjects with cardiac or pericardial disease added. Minor amendments to infusion reaction treatment guidelines for pembrolizumab.
Section 7.4.7 Monitoring for Encephalopathy Syndrome	New section added to describe monitoring for encephalopathy syndrome
Section 8.9 Pembrolizumab Symptom Management	Requirement for monitoring of subjects with pneumonitis added. Management of myocarditis added.
Section 8.10 Management of Encephalopathy Syndrome	New section added to describe management of encephalopathy syndrome
Section 9.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information	Clarification to ensure AEs and SAEs are collected until the end of the study in all subjects.
Section 9.2 Definition of AEs	Clarification of definition of AEs.
Section 9.3 Reporting Serious Adverse Events	Reporting requirements of SAEs to GSK added.

Section of Amendment No. 2.0	Change
Section 9.4 Reporting Criteria During Long-Term Follow-up (Years 1 to 15)	Reporting criteria amended. Clarification that SUSARs to be shared in the form of INDSRs.
Section 9.7 Regulatory Reporting Requirements for Serious Adverse Events	Clarification that SUSARs to be shared in the form of INDSRs.
Section 9.8 Cardiovascular and Death Events	Updated to include CV and death sections of the CRF to be completed.
Section 9.9 Pregnancy	Clarification for pregnancy reporting.
Section 9.13 Events of Clinical Interest	Clarification for ECI reporting.
Section 9.14 Timelines for Safety Reporting	Updated to include timelines for safety reporting for initial reports and follow-up information on previous reports.
Section 10.2 Safety Review Team	Minor revision to description of SRT to align with GSK terminology.
Section 16.1 List of Abbreviations and Definitions of Terms	Updated abbreviation list

Protocol v4.0 (Amendment 3)

Primary Reason for Amendment

Changes made to the protocol were requested by the FDA as a result of safety events which included 2 reports of Guillain-Barré syndrome in subjects who have received chemotherapy and NY-ESO-1^{c259}T during clinical trials.

Section of Amendment No. 3.0	Change
Synopsis Key Inclusion/Exclusion Criteria	Addition of 'Prior or active demyelinating disease as an exclusion criterion'.
3.6.2	Update to risk assessment to add additional risk of Guillain-Barré syndrome and other demyelinating neuropathies.
4.2	Addition of Prior or active demyelinating disease as an exclusion criterion.

Section of Amendment No. 3.0	Change
9.3	Addition of all cases of Guillain-Barré syndrome or acute demyelinating neuropathy as a reportable SAE within 24 hours.
10.2	Addition of Management and Monitoring for Demyelinating Neuropathy and other Neurological events
10.3.1	Addition of Mandated Study Pause due to GBS

Protocol v5.0 (Amendment 4)

Primary Reason for Amendment

Several changes related to FDA requests were made, including changes to Inclusion Criteria #5, the addition of study stopping rules, and the Encephalopathy (now Immune Effector Cell-Associated Neurotoxicity or ICANS) and the CRS grading and management criteria were updated. Also, changes were made to the lymphodepletion regimen for older subjects, and the randomization scheme was removed to enroll Arm1 (NY-ESO-1^{c259}T single infusion) subjects first.

Section of Amendment No. 4.0	Change
Synopsis and Section 3.1 and Throughout	Removal of subject randomization. Enrollment of Arm 1 will be completed before continuing enrolling subjects to Arm 2
Synopsis and Section 4.1	Updated Inclusion Criteria #5; removed PRMM and modified RRMM to only include subjects who have received at least 3 prior regimens. List of prior therapies has also been modified Updated Inclusion Criteria #10. Modified calculation for creatinine clearance
Synopsis and Section 4.2	Updated Exclusion Criteria #2 to note that it only applies to subjects that would be assigned to Arm 2 Updated Exclusion Criteria #3 for clarity Added new Exclusion Criteria #5 Updated Exclusion Criteria #13 to include GvHD

Section of Amendment No. 4.0	Change
	occurring post ASCT
Synopsis and Section 2	Updated subject population to those with relapsed refractory disease only
Synopsis, Section 11	Plans for statistical analyses extensively updated; futility analysis incorporated.
Section 4.1	Clarified Inclusion Criterion 5 with respect to prior therapy requirements
Section 4.2	Updated Exclusion Criterion 3 and corrected Exclusion Criterion 13
Section 4.7	Updated study stopping and pausing rules
Section 3.6.1	Updated section with final analysis data and reference
Section 5.4.1	Table 2 updated with currently available information.
Section 5.2	Added lymphodepleting regimen adjustments for subjects ≥ 60 years old history and for those with history of severe and prolonged cytopenia to improve subject safety
Section 7.1 and 7.5.3	Removed sequential sample collection for screening and clarified language regarding sample collection for consistency across study documents
Section 7.3 and 7.5.3	Updated scheduled bone marrow sampling from Week 6 to Week 3, unless the scheduled Week 3 infusion of pembrolizumab is delayed to Week 6
Section 8.2	Revised language according to GSK Safety Panel recommendations to align with other study protocols
Section 8.5	Revised management guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system

Section of Amendment No. 4.0	Change
Section 8. 9	Text updated with currently available information.
Section 8.10	Revised management guidelines to utilize the American Society for Transplantation and Cellular Therapy updated grading system [Lee, 2019]
Section 8.11	Added section for management of Guillain-Barré Syndrome (GBS)
Section 9.1 and Section 9.4	Modified AE and SAE collection times for the study; added delayed AE definition
Section 9.13	Additional ECIs were included to align with other study protocols as per GSK Safety Panel recommendations
Section 10.1.3.2	Removed the definition of clonality in relation to testing for insertional oncogenesis
Section 11.2	Added section regarding interim analysis

Protocol v6.0 (Amendment 5)

Primary Reason for Amendment

This amendment restructures the protocol for a clearer presentation of the 3-part study design. This amendment also introduces the intent to enroll, treat, and monitor for safety and efficacy subjects who have previously received a BCMA-targeted therapy as a separate line of therapy potentially in a separate clinical trial. In addition to other changes listed in the table below, this amendment updates several eligibility criteria and clarifies Section 3.3.1 to indicate that enrollment into Arm 2 only rather than enrollment into both arms would be paused following start of lymphodepletion of the third Arm 2 subject.

The following changes were implemented in Protocol Amendment 5.

Section of Amendment No. 5.0	Change
Change history, Section 3.1, Section 3.1 Figure 1 footnote, Section 3.1.2.2, Section 7 Figure 2 footnotes	Clarified that subjects may receive BCMA-targeted therapy as a distinct line of therapy between leukapheresis and lymphodepletion and that this therapy may be in a separate clinical trial. The subject must progress from this BCMA-targeted therapy prior

Section of Amendment No. 5.0	Change
	to receiving NY-ESO-1^{c259} T cell therapy.
Synopsis, Section 2	Added secondary endpoint to monitor persistence of NY-ESO-1^{c259}T cells and to evaluate potential correlation with safety, clinical response and phenotype of the infused T-cells.
Synopsis, Section 4.1.1	Modified Inclusion Criterion 5 to indicate that subjects must have received an alkylator as prior anti-cancer therapy unless the subject was ineligible to receive an alkylator or unless receipt of an alkylator was contraindicated for the given subject.
Synopsis, Section 4.1.1	Updated Inclusion Criterion 7 to include immuno-oncology agents overall in addition to checkpoint inhibitors
Synopsis, Section 4.1.3, Section 6.3.3	Updated Inclusion Criterion 16 to remove requirement for male subjects that contraception continue to be used for at least 4 months following last dose of pembrolizumab. This change brings this inclusion criterion into alignment with the current United States Prescribing Information for pembrolizumab.
Synopsis and numerous other points in the protocol where pembrolizumab dosing schedule discussed	Clarified pembrolizumab dosing schedule in the event of ongoing toxicities that would impact pembrolizumab treatment
Synopsis, Section 11	Clarified timing of primary data analysis from at least 6 months after last subject treated with NY-ESO-1^{c259}T to after the last subject treated with NY-ESO-1^{c259}T had undergone 3 disease assessments
Section 3.1	Clarified plan by which future subjects would be enrolled following removal of randomization in Protocol Amendment 4.
Synopsis, Section 3.4	Updated number of subjects enrolled per arm to permit adequate enrollment to support results analysis and clarified the types of subjects to be enrolled
Synopsis	Grouped inclusion criteria and exclusion criteria into Screening (Part 1), Leukapheresis (Part 2) and

Section of Amendment No. 5.0	Change
	Lymphodepletion and Treatment (Part 3) to correspond with three key portions of study
Synopsis, Section 4.1	Added inclusion criterion (13) for absolute neutrophil count (ANC), CD3 count, and lymphocyte count prior to leukapheresis
Synopsis, Section 4.1	Updated ANC and haemoglobin requirements (Inclusion criterion 14).
Synopsis, Section 4.1	Clarified contraception start times for males and females (Inclusion criterion 15)
Synopsis, Section 4.2	Clarified exclusion criterion 7 to be applicable not only to drugs similar to fludarabine or cyclophosphamide but to be applicable also to fludarabine and cyclophosphamide
Synopsis, Section 4.2	Add exclusion criterion 22 to impose a time limit for start of lymphodepletion relative to leukapheresis
Section 1.3	Added information about therapies targeting the anti-B cell maturation antigen (BCMA)
Section 1.5.2	Added rationale for treating patients previously treated with agent(s) targeting BCMA
Section 3.1	Clarified study's 3-part composition (screening, leukapheresis/manufacturing, and lymphodepletion/treatment) and added description of activities associated with each part
Section 3.1	Added clear definition of "enrolled"
Section 3.1	Added figure showing 3 key parts to study and subject path through study
Section 3.1 and Section 3.4	Clarified numbers of patients to be enrolled per arm and enrollment plan
Section 3.1.2.2	Added description of intermediate therapy, including timing and potential that intermediate therapy could be received while enrolled in an alternative study with another sponsor

Section of Amendment No. 5.0	**Change**
Section 3.3.1	Clarified that, after the third subject in Arm 2 has begun lymphodepletion, enrollment into Arm 2 would be paused until completion of the safety analysis for Arm 2 or unless a subject required replacement
Section 3.6.2	Updated risk information for NY-ESO-1^{c259}T, including information for adverse events of special interest
Section 3.6.2	Updated risk information for pembrolizumab interest
Synopsis, Section 4.1.3	Updated requirements for male contraception for Arm 2 subjects following last dose of pembrolizumab.
Section 4.6	Added “progressive disease” as a reason for discontinuing pembrolizumab.
Section 5.1	Clarified guidance on target apheresis collection and on potential for additional aphereses.
Section 5.2.1	Added new section with dose modification guidance for lymphodepletion of subjects ≥60 years of age
Section 5.3.2	Updated and streamlined cell infusion guidance, referring sites to Drug Product and Infusion Manual for details
Section 7	Moved study schematic from Section 3 to Section 7 to be closer to description of study procedures
Section 7.3 Table 3, and footnotes “a” and “ac” in Table 3	Updated “bone survey” to “bone imaging” to include not only bone survey, but also CT, PET, and MRI.
Section 7.3	Footnote “a”- clarified timing of test completion and sample collections
Section 7.3 Table 3, Section 7.5, Section 7.5.2	Added text describing sample collection purpose and schedule for soluble BCMA analysis to support predictions of patient outcomes
Section 7.5	Clarified that correlative studies would be performed on bone marrow aspirates – not from material collected by biopsy

Section of Amendment No. 5.0	**Change**
Section 7.5.3	Added additional guidance for collection of bone marrow aspirates
Section 9.1	Updated to clarify timing of AE/SAE collection and types of AE/SAE that are to be collected in Part 1, Part 2, and Part 3 and to specify how any safety event occurring during bridging therapy is to be recorded
Section 9.13	Updated categories / descriptions of Adverse Events of Special Interest (AESI)
Section 9.14	Updated safety reporting table to include guidance for reporting of AESI
Section 11	Updated data analysis approach and response assumptions
Section 11.1	Clarified all population definitions to make consistent with program definitions.
Section 11.2	Added conditions for conduct of interim analyses.
Section 11.3	Statistical section was re-evaluated and refocused on overall subject population (10 subjects per arm) rather than also on BCMA-treated subjects. Decision rules for futility determination were redefined. Conditions for study expansion were added
Section 7.4.8 and Appendix 16.5	Updated version of International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma from Rajkumar,2011 to Kumar, 2016 in Section 7.4.8. Deleted former Appendix 16.5 which included full IMWG Uniform Response Criteria for Multiple Myeloma, 2011. Deleted Rajkumar reference for 2011 version and added Kumar, 2016 reference.