Protocol Number GSK208466(ADP-04511)

A Pilot Study of Genetically Engineered NY-ESO-1 Specific NY-ESO-1^{c259} T cells in HLA-A2+ Patients with Synovial Sarcoma

CLINICAL STUDY PROTOCOL

A Pilot Study of Genetically Engineered NY-ESO-1 Specific (c259) T cells in HLA-A2+ Patients with Synovial Sarcoma

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CONFIDENTIALITY STATEMENT

DECLARATION

This study will be conducted in compliance with the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE
Aisha Hasan, MD	PPD	10/17/18

INVESTIGATOR

I agree to conduct this study in accordance with the design and specific provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in this protocol. I also agree to collect and handle all clinical specimens in accordance with the protocol. I have read and understand the contents of the Investigator's Brochure.

TYPED NAME	SIGNATURE	DATE

PPD

SUMMARY OF CHANGES

Primary reason for amendment

Protocol GSK208466 (ADP-4511) Version 15 (15-OCT-2018) includes changes made to the protocol 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 GSK3377794 during clinical trials.

PROTOCOL SYNOPSIS

Title

A Pilot Study of Genetically Engineered NY-ESO-1 Specific NY-ESO-1(c259) T cells in HLA-A2+ Patients with Synovial Sarcoma

Background

Patients with unresectable, metastatic and recurrent synovial sarcomas have long-term survival rates of <30%. Cytotoxic chemotherapy has not significantly improved survival for this high-risk group of patients.

A recent study (Robbins 2011) conducted by the NCI Surgery Branch demonstrated that adoptive immunotherapy using T cells genetically engineered to recognize NY-ESO-1 following lymphodepletion led to objective antitumor responses in four out of six patients with recurrent, metastatic synovial sarcoma.

Objectives

Primary:

Determine the response rate in patients with unresectable, metastatic or recurrent synovial sarcoma treated with lymphodepletion and Treg depletion followed by adoptive immunotherapy with T cells engineered to recognize an HLA-A2 restricted NY-ESO-1 derived peptide (Cohort 1).

Determine the response rate and duration of response of adoptive immunotherapy with NY-ESO-1^{c259}T cells in patients with synovial sarcoma and low-level expression of NY-ESO-1 (Cohort 2).

Determine the response rate and duration of response of adoptive immunotherapy with NY-ESO-1^{c259}T cells in patients with synovial sarcoma treated with a lymphodepleting regimen containing cyclophosphamide as a single cytotoxic agent (Cohort 3).

Determine the response rate and duration of response of adoptive immunotherapy with NY-ESO-1^{c259}T cells in patients with synovial sarcoma treated with a lymphodepleting regimen containing cyclophosphamide and fludarabine cytotoxic agents at reduced total doses relative to Cohort 1 (Cohort 4).

Secondary:

Determine the safety of treatment with adoptively transferred NY-ESO-1^{c259}T.

When possible, assess whether patients with progressive disease following NY-ESO-1^{c259}T or who do not respond (Cohort 3 and 4) experience a response following a second dose.

Exploratory:

Evaluate persistence, phenotype and functionality of adoptively transferred NY-ESO-1^{c259}T and correlate with clinical responses.

Evaluate mechanisms of resistance and sensitivity to NY-ESO-1^{c259}T.

Evaluate antigen spreading as a mechanism of response.

Eligibility

Inclusion Criteria

1. Pathologically or histologically confirmed synovial sarcoma that has been treated with a standard chemotherapy regimen containing ifosfamide and/or doxorubicin, is intolerant of or not actively responding to this regimen (i.e. the patient should not be taken prematurely off their primary regimen if they are continuing to respond to it) and remains:
    - unresectable or (intent is not to enroll patients with resectable tumors)
    - metastatic or
    - progressive/persistent or recurrent
2. Patients must have measurable disease in order to allow assessment of an anti-tumor response. See Section 5.4.
3. Pathologic review by a central laboratory designated by the Sponsor and confirming NY-ESO-1 expression by immunohistochemistry (IHC). Patients must have proven positive tumor sample for NY-ESO-1 as follows:

Cohort 1

Positive expression is defined as 2+ or 3+ by IHC in ≥ 50% cells

Cohort 2

Positive expression is defined as ≥ 1+ by IHC in ≥ 1% cells but not to exceed 2+ or 3+ in ≥ 50% cells

Cohort 3

Positive expression is defined as 2+ or 3+ by IHC in ≥ 50% cells

Cohort 4

Positive expression is defined as 2+ or 3+ by IHC in ≥ 50% cells

4. HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 by high resolution testing
5. Patient is ≥4 years of age on the day the Informed Consent is signed.
6. Patients must be >18 kg, for apheresis safety purposes.
7. Patients may have received salvage chemotherapy or other therapies. Prior Therapies:

All previous cytotoxic chemotherapy, monoclonal antibody therapy, or immune therapy should be washed out 3 weeks before apheresis and must be completed at least 3 weeks prior to pre-infusion lymphodepleting chemotherapy.

Systemic corticosteroid or other immunosuppressive therapy should be washed out 2 weeks before apheresis and must be completed at least 2 weeks prior to pre-infusion lymphodepleting chemotherapy.

Biologic or other approved molecular targeted small molecule inhibitors should be washed out 1 week or 5 half-lives (whichever is longer) before apheresis and must be completed at least 1 week or 5 half-lives (whichever is longer) prior to pre-infusion lymphodepleting chemotherapy.

Any grade 3 or 4 hematologic toxicity of previous therapy must have resolved to grade 2 or less (or to values specified below) prior to apheresis and any grade 3 or 4 toxicity must have resolved to grade 2 or less (or to values specified below) prior to pre-infusion lymphodepleting chemotherapy.

8. Performance status: ECOG 0-1, or for children ≤10 years of age, Lansky >60 (Appendix 1).
9. Life expectancy >3 months.
10. Patient must have adequate organ function as indicated by the following laboratory values in the table below:

System	Laboratory Value
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.0 x10^9/L
Platelets	≥ 75 x10^9/L (not achieved by transfusion)
Renal	
Creatinine clearance ≥ 40 ml/min Patients <65 yrs of age can be assessed using estimated creatinine clearance calculated using the Cockcroft and Gault formula: $\text{Creatinine clearance} = \frac{(140 - \text{age}) * \text{weight kg}}{72 * \text{serum creatinine mg/dl}} (* 0.85 \text{ in females})$ Patients ≥65 yrs 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.	
Cardiac	
Left ventricular ejection fraction	≥40%, or Fractional Shortening ≥28%

11. Ability to give informed consent prior to any study-specific procedures. Any standard of care procedures (e.g., lab tests, scans) can be used for purposes of assessing study eligibility as long as all other requirements as stated in the protocol are met. For patients <18 years of age (or the legal minimum are in the relevant country) their legal guardian must give informed consent. Pediatric patients will be included in age-appropriate discussion in order to obtain verbal assent.
12. Male or Female. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 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 another 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.
    - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

b. Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    - Is not a WOCBP as defined in Section 2.3.1.

    OR

    - Is a WOCBP (as defined in Section 2.3.1) 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 2.3.1 during the intervention period 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. A 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 participant must be excluded from participation if the serum pregnancy result is positive.

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

Exclusion Criteria:

1. **ALT** >2.5xULN without documented liver metastases/tumor infiltration.

   OR

   Total Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

2. 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.

3. Clinically significant systemic illness (e.g. serious active infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the judgment of the PI would compromise the patient's ability to tolerate protocol therapy or significantly increase the risk of complications.

4. Untreated CNS metastasis. Extradural masses that have not invaded the brain parenchyma or parameningeal tumors without evidence for leptomeningeal spread will not render the patient ineligible. Patients with previous CNS tumor involvement that has been treated and is stable for at least 6 weeks are eligible.

5. Previous treatment with genetically engineered NY-ESO-1 specific T cells.

6. Pregnant or breastfeeding females (due to risk to fetus or newborn).

7. Uncontrolled intercurrent illness including, but not limited to:

   a) Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class >1.

   b) Uncontrolled clinically significant arrhythmia in last 6 months.

   c) Acute coronary syndrome (angina or myocardial infarction) in last 6 months.

   d) Severe aortic stenosis, symptomatic mitral stenosis

   e) Prior or active demyelinating disease.

8. 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).

9. Active HIV, HBV, HCV or HTLV 1 or 2 infection as defined below (due to increased risk of complications during the lymphodepleting regimen and confounding effects on the immune system):
    - 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 study treatment. For potent immunosuppressive agents, subjects with presence of hepatitis B core antibody (HBcAb) should also be excluded.
    - Active hepatitis C subjects as demonstrated by test for hepatitis C RNA. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. Eligibility will be determined based on a negative screening value.
    - Positive serology for HTLV 1 or 2.
10. Subject has history of active, chronic or recurrent (within the last year prior to enrolment) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments.

Design

Patients will undergo apheresis at the enrolling institution. PBMCs will be shipped to a central manufacturer for gene transduction, activation and expansion, then cryopreserved and shipped back to the enrolling institution.

Patients will undergo lymphodepletion with cyclophosphamide with or without fludarabine as outlined in the Treatment Schema. Patients will receive transduced NY-ESO-1^{c259}T. Cell doses are specified in Section 3.2.7

The trial seeks to enroll up to 20 patients into Cohort 1 and up to 15 patients each into Cohorts 2 - 4. See Section 3.2 and Section 6.

Cohort 1: Complete. Patients must have proven positive, high tumor expression of NY-ESO-1 defined as 2+ or 3+ by immunohistochemistry (IHC) in ≥ 50% cells. Patients receive Regimen A lymphodepletion.

Cohort 2: Closed to enrollment. Up to 15 patients may be treated with NY-ESO-1^{c259}T. Patients must have proven positive, low tumor expression of NY-ESO-1 defined as ≥ 1+ by IHC in ≥ 1% cells but not to exceed 2+ or 3+ in ≥ 50% cells. Patients receive Regimen A lymphodepletion. Up to an additional 5 patients considered unsuitable for Regimen A

for reasons that include, but are not limited to, advanced age, extent of prior therapies, or presence of co-morbidities may be enrolled to receive Regimen C.

Cohort 3: Closed to enrollment. Up to 15 patients may be enrolled to achieve at least 10 patients treated with NY-ESO-1^{c259}T at a prespecified cell dose. Patients must have proven positive, high tumor expression of NY-ESO-1 defined as 2+ or 3+ by IHC in ≥ 50% cells. Patients receive Regimen B lymphodepletion.

Note: If insufficient activity is seen using cyclophosphamide-only lymphodepletion in cohort 3 and in combination with data across the Sponsor program using this regimen, Cohort 3 will cease enrolling and close. Patients previously eligible for Cohort 3 will be enrolled to Cohort 4. Cohort 4 is now open as Cohort 3 is closed. See Section 3.2.3

Cohort 4: Closed to enrollment. Up to 15 patients may be treated with NY-ESO-1^{c259}T. Patients must have proven positive, high tumor expression of NY-ESO-1 defined as at least ≥ 50% of cells that are 2+ and/or 3+ by IHC. Patients receive Regimen C lymphodepletion.

Note: If insufficient activity is seen using reduced dose Regimen C lymphodepletion in Cohort 4, the cohort will cease enrolling and close. The decision will be based on clinical judgment. If the anti-tumor activity with Regimen C is determined to be suboptimal, then future subjects enrolled in Cohort 4 will receive Regimen A. See Section 3.2.4.

Patients ≥40kg will receive the minimum cell dose of at least 1x10^9 transduced NY-ESO-1^{c259}T cells with a maximum of 6x10^9 transduced cells. The target dose for this protocol is 5x10^9 transduced NY-ESO-1^{c259}T 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 1 x 10^9 – 6 x 10^9 range.

Patients <40 kg will be dosed per body weight with a minimum 0.025x10^9 transduced cells/kg, with a target dose of 0.125x10^9 transduced cells/kg.

Patients will be monitored for toxicity, antitumor effects and immune endpoints.

Patients who have a confirmed response, or have stable disease for >3 months and then progress, may receive a 2nd cycle of treatment, provided eligibility criteria are met. The 2nd cycle of treatment following a confirmed response or stable disease will use the same lymphodepleting chemotherapy regimen as the first cycle of treatment. Patients who meet the eligibility criteria may receive a 2nd treatment of NY-ESO-1^{c259}T no sooner than 60 days and no later than 2 years following completion of the first treatment. Patients in Cohort 3 and 4 who do not show a response to treatment may receive a second dose of NY-ESO-1^{c259}T using Regimen A lymphodepletion. Refer to Section 3.5.3 for information on eligibility for and details of second infusions.

Treatment Schema

At Apheresis: Collect 1x10^8 PBMC/kg target (minimum 1.5x10^7 PBMC/kg) at participating site.

Lymphodepletion

Regimen A			
Day	**Drug**	**Dose**	**Route**
-5	**Fludarabine**	30 mg/m^2	IV
-4	**Fludarabine**	30 mg/m^2	IV

-3	**Fludarabine**	30 mg/m^2	IV
	Cyclophosphamide	1800 mg/m^2	IV
-2	**Fludarabine**	30 mg/m^2	IV
	Cyclophosphamide	1800 mg/m^2	IV
0	**NY-ESO-1^{c259}T infusion**		

Regimen B			
Day	**Drug**	**Dose**	**Route**
-3	**Cyclophosphamide**	1800 mg/m^2	IV
-2	**Cyclophosphamide**	1800 mg/m^2	IV
0	**NY-ESO-1^{c259}T infusion**		

Regimen C			
Day	**Drug**	**Dose**	**Route**
-7	**Fludarabine**	30 mg/m^2	IV
	Cyclophosphamide	600 mg/m^2	IV
-6	**Fludarabine**	30 mg/m^2	IV
	Cyclophosphamide	600 mg/m^2	IV
-5	**Fludarabine**	30 mg/m^2	IV
	Cyclophosphamide	600 mg/m^2	IV
0	**NY-ESO-1^{c259}T infusion**		

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1.1 Objectives

1.1.1 Primary

- Determine the response rate in patients with unresectable, metastatic or recurrent synovial sarcoma treated with lymphodepletion and Treg depletion followed by adoptive immunotherapy with T cells engineered to recognize an HLA-A2 restricted NY-ESO-1 derived peptide (Cohort 1)
- Determine the response rate and duration of response of adoptive immunotherapy with NY-ESO-1^{c259}T cells in patients with synovial sarcoma and low-level expression of NY-ESO-1 (Cohort 2)
- Determine the response rate and duration of response of adoptive immunotherapy with NY-ESO-1^{c259}T cells in patients with synovial sarcoma patients treated with a lymphodepleting regimen containing cyclophosphamide as a single cytotoxic agent (Cohort 3)
- Determine the response rate and duration of response of adoptive immunotherapy with NY-ESO-1^{c259}T cells in patients with synovial sarcoma treated with a lymphodepleting regimen containing cyclophosphamide and fludarabine cytotoxic agents at reduced total doses (Cohort 4)

1.1.2 Secondary

- Determine the safety of treatment with adoptively transferred NY-ESO-1^{c259}T.
- When possible, assess whether patients with progressive disease following NY-ESO-1^{c259}T or who do not respond (Cohorts 3 and 4) experience a response following a second dose

1.1.3 Exploratory

- Evaluate persistence, phenotype and functionality of adoptively transferred NY-ESO-1^{c259}T and correlate with clinical responses
- Evaluate mechanisms of resistance and sensitivity to NY-ESO-1^{c259}T
- Evaluate antigen spreading as a mechanism of response

1.2 Endpoints

1.2.1 Primary Endpoints

The following endpoints will be evaluated in each cohort:

- Objective Response Rate for each cohort per RECIST v1.1

1.2.2 Secondary Endpoints

The following endpoints will be evaluated in each cohort:

1.2.2.1 Efficacy Endpoints

- Duration of overall response per RECIST v1.1
- Progression free survival per RECIST v1.1
- Best Overall Response
- Overall Survival

1.2.2.2 Safety Endpoints

- AEs, including SAEs
- Laboratory assessments, including chemistry, hematology, coagulation and anti-infused cell (NY-ESO-1^{c259}T) antibodies
- Correlate circulating cytokines with cytokine release syndrome
- Correlate persistence of NY-ESO-1^{c259}T over time with safety parameters

1.2.3 Exploratory Endpoints

The following endpoints will be evaluated in each cohort:

- Objective Response Rate for subjects who receive a second infusion of NY-ESO-1^{c259}T
- Determine whether loss of NY-ESO-1 in the tumor is a mechanism of resistance
- Correlate biomarkers in tumor tissue and blood with response following infusion of NY-ESO-1^{c259}T
- Correlate persistence, phenotype and functionality of NY-ESO-1^{c259}T in the blood and or tumor with response to treatment
- Correlate clonal outgrowth, phenotype and activity of T cell populations with response following infusion of NY-ESO-1^{c259}T
- Determine whether T cell clonal outgrowth or enhancement of the endogenous anti-tumor immune response occurs following infusion of NY ESO 1^{c259}T

1.3 Background and Rationale

1.3.1 Synovial Sarcoma

Synovial sarcomas account for approximately 6%–10% of all soft tissue sarcomas. Approximately 33% of synovial sarcomas occur in childhood, and approximately 20-25% of non-rhabdomyosarcoma soft tissue sarcomas occurring in childhood are synovial sarcomas. The peak incidence is in the third decade of life, and approximately 70% of patients with synovial sarcoma are less than 40 years of age. Thus synovial sarcoma is primarily a disease of children and young adults (Herzog 2005).

The most common primary site for synovial sarcoma is the distal lower extremity (63%) with a tendency for primary tumors to develop near the knee or ankle. Synovial sarcomas also often

present as painless masses in the upper extremity, head, neck and trunk. The lungs are a common site for distant metastases, occurring in 6% of patients in a recent series (Ferrari 2004). Synovial sarcoma metastasizes to the lymph nodes more frequently than most sarcomas, with clinically evident lymph node metastases reported in 14-20% of cases (Tunn 2008).

Histologically, synovial sarcoma consistently demonstrates a spindle cell fibrous stromal component, and a variable epithelial glandular component. Tumors comprised exclusively of the spindle cell histology are classified as monophasic, whereas those comprised of spindle cell and epithelial components are classified as biphasic. Immunohistochemistry typically reveals expression of keratin in the spindle cell component and epithelial membrane antigen in the epithelial component.

A pathognomonic chromosomal translocation between chromosome X and 18 is found in virtually all cases of synovial sarcoma. The translocation involves the *SYT* gene at 18q11 and the *SSX1*, *SSX2*, or *SSX4* gene at Xp11 (Clark 1994; de Leeuw 1995; Crew 1995). The fusion transcript is found in both the spindle cell and epithelioid cells. There is no clear evidence that the fusion partner effects prognosis, but the fusion partner does have a clear impact on histology and epidemiology, because essentially all *SYT-SSX2*$^{+}$ tumors are monophasic (Kawai 1998) and there is an even male-to-female ratio for *SYT-SSX1* but a 1:2 ratio for *SYT-SSX2*. Haldar et al. modeled synovial sarcoma in mice by expressing the *SYT-SSX* translocation in myoblasts (Haldar 2007). The fusion protein was oncogenic only when expressed in myoblasts, but not when expressed earlier or later in myogenesis, suggesting that the myoblast may be the cell of origin (Davis 2007). Interestingly, even in mouse model of synovial sarcoma, the majority of tumors occur near a joint, suggesting that microenvironmental factors in this area are uniquely suited to support growth of SYT-SSX tumors.

Like all soft tissue sarcomas, therapy for synovial sarcoma is largely focused on surgical excision with wide margins. Indeed, synovial sarcoma does not appear to be curable without complete surgical excision and very few patients with distant metastases or recurrent synovial sarcoma are cured with standard therapies, regardless of the administration of chemotherapy (discussed below). Microscopic or macroscopic residual tumor is consistently an adverse prognostic factor (Andrassy 2002; Andrassy 2001), therefore, excisions with margins <3 cm should be considered for second excision if possible without severe functional limitation. Tumor size is an important prognostic factor as well. The 5-year event-free survival rate was 66% in 86 patients with <5 cm sized SS treated in Milan compared with a rate of 24% for synovial sarcoma >5 cm^{2}. Adjuvant radiation therapy to 50-70 Gy provides a benefit in terms of the local control for patients with synovial sarcoma (Okcu 2001). As a result, adjuvant radiation therapy is often recommended for synovial sarcomas >5 cm in maximal diameter (Wolden 2005). In summary, size of tumor (>5 cm), axial location, high grade (grade 3), invasiveness of tumor, and detection of distant metastases are poor prognostic factors (Ferrari 2004; Okcu 2003; Ferrari 2008; Sultan 2009; Canter 2008).

Neoadjuvant or adjuvant chemotherapy for synovial sarcoma remains an area of controversy. Compared with other spindle cell sarcomas, synovial sarcoma appears to be somewhat more chemosensitive, with objective responses to chemotherapy reported in 40%–60% (Ferrari 2004; Pappo 2005). Prior to the initiation of the EPSSG NRSTS trials, all pediatric patients with synovial sarcoma enrolled in European trials received chemotherapy regardless of stage, with the same regimen used for rhabdomyosarcoma. A retrospective study of this cohort that sought to investigate the potential impact of cytotoxic chemotherapy in this disease reported longer survival for children receiving adjuvant chemotherapy when tumors were >5 cm and high grade (Ferrari

2004), but no difference in survival with adjuvant chemotherapy in patients with smaller tumors or low grade tumors. Similarly, a multicenter, multivariate review of pediatric synovial sarcoma patients by Okcu et al. revealed that chemotherapy responses resulted in longer survival in clinical group III patients (Okcu 2003). Thus, although randomized studies have not been undertaken, most pediatric oncologists recommend neoadjuvant or adjuvant chemotherapy for children with high-risk synovial sarcoma. High-risk is typically defined as high-grade histology and size >5 cm or axial primary, or metastatic disease.

Some recent non-randomized analyses of adult patients with synovial sarcomas >5 cm also report a survival advantage for patients treated with ifosfamide-containing regimens (Canter 2008; Eilber 2007). However, other reviews of synovial sarcoma in adults have not shown a positive effect of chemotherapy (Palmerini 2009). In a non-randomized study from Milan, chemotherapy appeared to improve survival in synovial sarcoma, regardless of size, for younger patients (0–16 years old), but did improve overall survival rates in patients >17 years old, suggesting that age may influence clinical behavior of synovial sarcoma (Ferrari 2004). Indeed, differences in the 5-year survival curves for pediatric synovial sarcoma (60%–83%) versus adult synovial sarcoma (50%–70%) suggest that older age itself may be an adverse risk factor (Sultan 2009; Palmerini 2009). This is not likely accounted for by different attitudes regarding chemotherapy, since a SEER analysis showed that the 0- to 9-year-old age group had better outcomes than the 10- to 18-year-old age group, who were likely to have been treated in a similar fashion (Sultan 2009). Similar adverse effects of age on prognosis are seen in Ewing's sarcoma, although the basis for this remains unclear and there are no known age associated biologic differences in synovial sarcoma.

In summary, the consensus regarding chemotherapy is not clear for adult patients with high-risk synovial sarcoma, but it is clear that unresectable, metastatic and recurrent synovial sarcomas are nearly universally fatal. Thus, new therapies are needed for patients with these high-risk features.

1.3.2 Adoptive Immunotherapy with NY-ESO-1 Specific T Cells in Synovial Sarcoma

NY-ESO-1 is a member of the cancer-testis family of tumor antigens. NY-ESO-1 is expressed in approximately 70-80% of cases of synovial sarcoma, reportedly at high levels. Scanlan et al (2002) reported that in synovial sarcoma 16/ 21 specimens showed diffuse homogeneous staining but in 5 specimens (23%) this was heterogeneous. Lai et al (2012) evaluated NY-ESO-1 expression by immunohistochemistry in 417 tumors including 50 stage IV synovial sarcomas and reported that 38/ 50 (76%) expressed NY-ESO-1 in a strong and diffuse pattern (2-3+, >50–70% of tumor cells), 3 cases showed weak and focal expression (1+ <10% tumor cells) and 9 cases were negative for NY-ESO-1. Endo et al (2015) reported NY-ESO-1 staining intensity of 2 – 3+ by immunohistochemistry in >50% of tumor cells in 34/69 (49.3%) synovial sarcomas.

An HLA-A2 binding peptide corresponding to amino acids 157 to 165 of NY-ESO-1 (SLLMWITQC) can be recognized by NY-ESO-1 reactive T cells (Zeng 2002) and NY-ESO-1 epitopes are also recognized in the context of multiple HLA class II restriction elements (Jager 1998; Jager 2000). Several studies have demonstrated antibodies against NY-ESO-1 in patients with cancer. In one study, 10 out of 12 patients bearing NY-ESO-1 positive tumors demonstrated antibodies directed against this antigen (Gnjatic 2006), suggesting that among tumor associated antigens, NY-ESO-1 may be particularly immunogenic. Tumor vaccine trials have immunized with immunodominant Class I and II restricted peptides as well as recombinant NY-ESO-1 proteins. Thus far, clinical responses have been observed in a small percentage of patients treated with NY-ESO-1 vaccines alone (Bioley 2009; Old 2008).

Recently, T cells recognizing the immunodominant class I restricted HLA-A2 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-A2. The result is a high affinity T cell receptor designated as 1G4a95:LY TCR (c259 TCR), which shows pre-clinical activity *in vitro* and *in vivo* against NY-ESO-1 expressing HLA-A2+ tumors (Robbins 2008). The 1G4a95:LY TCR mediates efficient recognition by CD8+ T cells of the HLA-A2 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-A2 (Robbins 2008). This co-receptor independent recognition implies high avidity of the 1G4a95:LY TCR, a potentially important property of clinically active T cell receptors. The enhanced TCR binds with varying affinity to HLA-A2 subtypes. There is not much data evaluating the TCR in subtypes other than HLA-A201, but binding affinities are similar for HLA-A201 and HLA-A205, whereas binding to HLA-A206 is much higher.

Between 2008 and 2010 a clinical trial of adoptive immunotherapy following lymphodepletion using T cells expressing IG4a95:LY TCR was carried out in the Surgery Branch of the National Cancer Institute. Patients with NY-ESO-1 expressing tumors refractory to standard therapy were eligible

Patients with HLA-A2+, NY-ESO-1 synovial sarcomas and melanomas underwent apheresis for collection of mononuclear cells. They then received lymphodepletion with cyclophosphamide (60 mg/kg/d x2) and fludarabine (25mg/m^2/d x 5). PBMC were treated with anti-CD3 antibody and transduced with a retrovirus encoding 1G4a 95:LY TCR. A secondary T cell expansion was carried out with anti-CD3 antibody, and a median of 5x10^{10} T cells were generated for therapy (range 1.6 x 10^9 – 13 x 10$^{\mathbf{10}}$; approximately 1.9 x 10^9/kg- 2.2 x 10^8/kg). A median of 78% (range 63-87%) of the transferred CD8+ T cells and 65% (range 57-79%) of the transferred CD4+ T cells bound the NY-ESO-1 tetramer, and median of 92% (range 85-96%) of the total CD3+ T cells bound an anti-BV13.1 antibody, which binds the beta chain on the genetically transduced TCR. With the exception of one patient, the cell infusions were comprised of >67% CD8+ T cells. Lower, but substantial levels, also bound the NY-ESO-1 tetramer and all of the products recognized peptide pulsed target cells at concentration of 0.1-0.01 nM of NY-ESO-1:157-165. NY-ESO-1 specific T cells were infused after conditioning, then high dose IL2 was administered every 8 hours to tolerance (Robbins 2011; Robbins 2015).

The cell dose for the initial pilot study (Cohort 1) of GSK208466 (ADP-04511) protocol was chosen to largely replicate the doses administered in the Robbins et al study (Robbins 2011). The 4 patients with synovial sarcoma in that study who had clinical responses following treatment with NY-ESO-1 specific T cells received absolute doses ranging from 16-83 x 10^9 cells. Assuming average weights of 70 kg, this translates to a dose of 0.2-1 x 10^9/kg. No toxicity attributed to the cells was reported in that study and the goal in the current study is to replicate the cell product as closely as possible. Therefore, a target dose of 5x10^9 transduced cells was chosen with a minimum of 1x10^9 transduced cells and a maximum overall dose of 6x10^9 cells as it falls closely within the cell dose where clinical responses without significant toxicity were observed.

A recent update to the study reported 11 of 18 patients (61%) with synovial sarcoma and 11 of 20 patients (55%) with melanoma demonstrated objective clinical responses. The estimated overall three and five year survival rates for patients with synovial cell sarcoma were 38% and 14%, respectively, while the corresponding estimated survival rates for patients with melanoma were both 33% (Robbins 2015).

1.3.3 GSK208466(ADP-04511) Study Progress

As of February 2017, 36 patients were enrolled. 15 of these patients were enrolled in Cohort 1 (completed enrolment), 5 patients in Cohort 3 (completed enrollment) and 16 have been enrolled in Cohorts where enrolment is ongoing (6 subjects in Cohort 2 and 10 subjects in Cohort 4).

The following is a brief summary of Cohort 1. Patients with unresectable, metastatic or recurrent synovial sarcoma underwent lymphodepletion with 30 mg/m^2 fludarabine daily on days -5 through -2, and 1800 mg/m^2 cyclophosphamide daily on days -3 and -2 prior to NY-ESO-1^{c259}T administration on day 0. 119 patients were screened to identify 15 patients who were fully eligible and were enrolled in Cohort 1. Three of these patients were unable to receive NY-ESO-1^{c259}T cell infusion due to disease progression between the time of screening prior to apheresis and the baseline assessment prior to lymphodepletion. 12 patients received NY-ESO-1^{c259}T. 2 of these patients had poor cell growth and did not meet the minimum dose requirement of 1x10^9 transduced cells. Protocol exceptions were granted for each of these 2 patients to infuse these cells despite not meeting minimum dose requirements, and these patients are considered fully evaluable for safety endpoints. As a result, 10 patients meet the minimum requirements defined at the time of protocol design for efficacy evaluation of the 15 enrolled, therefore Cohort 1 has completed enrollment and is now closed. Of the 10 patients who received 1x10^9 transduced cells, 6 have a confirmed response per RECIST: 1 patient had a complete response (CR) which was maintained from month three up to month nine before relapse. In 5 patients with partial response (PR), the response continued for up to four to 10 months.

Preliminary safety data in 16 subjects who have received T-cell infusion (including 12 subjects in Cohort 1 and 4 in subsequent Cohorts) is briefly summarized (from Investigator Brochure dated 12 April 2016). The most common adverse events (non-laboratory) occurring in more than 5 subjects include nausea, pyrexia, cough, dyspnea, diarrhea, fatigue, dizziness, headache, rash maculo-papular, sinus tachycardia, vomiting, musculoskeletal pain, anxiety, constipation, cytokine release syndrome and pruritus. Cytokine Release Syndrome (CRS) was reported in 6 patients; in 3 patients this was Grade 3 or 4. Laboratory abnormalities reported as Grade ≥3 treatment related adverse events in 2 or more subjects include anemia, lymphocyte, neutrophil, platelet and white blood cell counts decreased, and hypophosphatemia. Serious AEs (SAE) reported in 2 or more subjects include pyrexia, cytokine release syndrome, febrile neutropenia, neutrophil count decrease, dyspnea, lymphocyte count decrease, and platelet count decrease. One fatal SAE of bone marrow failure (reported as bone marrow hypocellular and aplastic anemia) was reported in a patient enrolled in Cohort 2.

In addition, one subject in the ATTACK-OG clinical trial sponsored by The Christie Hospital NHS Foundation Trust [NCT01795976] experienced fatal gastrointestinal bleeding with gangrenous necrosis of the small bowel in the setting of rash, enterocolitis and bone marrow failure after initial bone marrow recovery.

As of January 2017, 64 patients have been treated in Sponsored NY-ESO-1^{c259}T studies. Please refer to the NY-ESO-1^{c259}T Investigator Brochure for additional information.

1.3.4 Optimization of Lymphodepletion

Animal studies and numerous clinical trials have documented the capacity for a “preparative regimen” to augment the efficacy of adoptive cell therapy (Dudley 2002). The biological effects of such “preparative regimens” are likely manifold, and it remains unclear which of these effects

is necessary and/or sufficient to augment immunotherapy efficacy (Klebanoff 2005). Current paradigms hold that "preparative regimens" augment expansion of adoptively transferred T cells by induction of T cell lymphopenia, which results in increased levels of homeostatic cytokines including interleukin-7 and interleukin-15, which sustain T cell proliferation (Fry 2001; Fry 2001; Cui 2009; Gattinoni 2005). Lymphodepleting regimens also induce transient reductions in suppressive T cell populations, which may augment proliferation of adoptively transferred T cells; however it is unclear which cytotoxic agents best achieve this. Lymphodepleting regimens may also induce damage to the lining of the gastrointestinal tract, which could allow transit of lipopolysaccharide across the mucosal barrier and may augment innate immunity, which may in turn augment T cell proliferation. Cytotoxic regimens also induce reductions granulocytic and monocytic hematopoietic cells, which may modulate suppressive effect of myeloid derived suppressor cells. Finally, cytotoxic agents may also induce tumor cell death within the microenvironment, which may render it more accessible to antigen activated T cells. Given that the primary factor responsible for augmenting expansion of adoptive transferred T cells remains unclear, it is not surprising that we have a limited understanding of which preparative regimens are most effective in this regard.

This clinical trial utilized lymphodepletion in Cohort 1 designed primarily to induce T cell depletion by use of both cyclophosphamide and fludarabine, a common conditioning strategy in recent gene modified adoptive T cell research. Some evidence indicates that cyclophosphamide as a single agent might achieve depletion of Treg lymphocytes without global depletion of the lymphocyte compartments, therefore reducing the depth of immunosuppression caused by lymphodepleting chemotherapy (Klebanoff 2005); however in some circumstances Tregs can be resistant to cyclophosphamide and this is thought to be the mechanism for efficacy of cyclophosphamide in graft-versus-host disease prophylaxis in the post- allogeneic transplant setting (Kanakry 2013). In order to establish whether cyclophosphamide alone can deliver an environment that allows activity of the therapeutic cells without the potential additional toxicity of an additional chemotherapeutic agent, Cohort 3 of this study and other Sponsor studies are evaluating the use of cyclophosphamide as a single-drug lymphodepleting regimen.

Recent evidence suggests that preparation for successful engraftment and expansion of gene modified adoptive cellular therapy may depend 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 a chimeric antigen receptor showed increased T cell expansion, persistence and disease-free survival when fludarabine was added in to a previously cyclophosphamide-only preparative regimen (Turtle 2015). Based on this emerging data, in light of our previous demonstrated efficacy in cohort 1, if there is insufficient activity in Cohort 3 and across the Sponsor's NY-ESO-1 program using cyclophosphamide as a single drug agent we will cease evaluating this option.

The lymphodepleting regimen in Cohort 1 in which objective tumor responses have been observed used a cyclophosphamide dose of 1800 mg/m^2/day for 2 days, in addition to fludarabine 30 mg/m^2/day for 4 days. This is a similar regimen to that used in reduced-intensity conditioning for hematopoietic stem cell transplantation (Paplham 2014), and while effective it has not been established that this is the best preparative strategy. Effective lymphodepletion has been demonstrated in studies using chimeric antigen receptors using reduced cyclophosphamide dosing than previously used in this study, together with fludarabine (Batlevi 2016). In Cohort 4, in order to establish whether efficacy can be maintained with less intensive lymphodepleting

chemotherapy, we will assess a fludarabine-cyclophosphamide combination regimen at a reduced total dose of each drug.

2 Eligibility Assessment and Enrollment

2.1 Inclusion Criteria

1. Pathologically or histologically confirmed synovial sarcoma that has been treated with a standard chemotherapy regimen containing ifosfamide and/or doxorubicin, is intolerant of or not actively responding to this regimen (i.e. the patient should not be taken prematurely off their primary regimen if they are continuing to respond to it) and remains:
    - unresectable or (intent is not to enroll patients with resectable tumors)
    - metastatic or
    - progressive/persistent or recurrent
2. Patients must have measurable disease in order to allow assessment of an anti-tumor response. See Section 5.4.
3. Pathologic review by a central laboratory designated by the Sponsor and confirming NY-ESO-1 expression by immunohistochemistry (IHC). Patients must have proven positive tumor sample for NY-ESO-1 as follows:

    Cohort 1

    Positive expression is defined as 2+ or 3+ by IHC in ≥ 50% cells

    Cohort 2

    Positive expression is defined as ≥ 1+ by IHC in ≥ 1% cells but not to exceed 2+ or 3+ in ≥ 50% cells

    Cohort 3

    Positive expression is defined as 2+ or 3+ by IHC in ≥ 50% cells

    Cohort 4

    Positive expression is defined as 2+ or 3+ by IHC in ≥ 50% cells
4. HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 by high resolution testing
5. Patient is ≥4 years of age on the day the Informed Consent is signed.
6. Patients must be >18 kg, for apheresis safety purposes.
7. Patients may have received salvage chemotherapy or other therapies. Prior Therapies:

    All previous cytotoxic chemotherapy, monoclonal antibody therapy, or immune therapy should be washed out 3 weeks before apheresis and must be completed at least 3 weeks prior to pre-infusion lymphodepleting chemotherapy.

    Systemic corticosteroid or other immunosuppressive therapy should be washed out 2 weeks before apheresis and must be completed at least 2 weeks prior to pre-infusion lymphodepleting chemotherapy.

Biologic or other approved molecular targeted small molecule inhibitors should be washed out 1 week or 5 half-lives (whichever is longer) before apheresis and must be completed at least 1 week or 5 half-lives (whichever is longer) prior to pre-infusion lymphodepleting chemotherapy.

Any grade 3 or 4 hematologic toxicity of previous therapy must have resolved to grade 2 or less (or to values specified below) prior to apheresis and any grade 3 or 4 toxicity must have resolved to grade 2 or less (or to values specified below) prior to pre-infusion lymphodepleting chemotherapy.

8. Performance status: ECOG 0-1, or for children ≤10 years of age, Lansky >60 (Appendix 1).
9. Life expectancy >3 months.
10. Patient must have adequate organ function as indicated by the following laboratory values in the table below:

System	**Laboratory Value**
Hematological	
Absolute Neutrophil count (ANC)	≥ 1.0 x10^9/L
Platelets	≥ 75 x10^9/L (not achieved by transfusion)
Renal	
Creatinine clearance ≥ 40 ml/min Patients <65 yrs of age can be assessed using estimated creatinine clearance calculated using the Cockcroft and Gault formula: $\text{Creatinine clearance} = \frac{(140 - \text{age}) * \text{weight kg}}{72 * \text{serum creatinine mg/dl}} (* 0.85 \text{ in females})$ Patients ≥65 yrs 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.	
Cardiac	
Left ventricular ejection fraction	≥40%, or Fractional Shortening ≥28%

11. Ability to give informed consent prior to any study-specific procedures. Any standard of care procedures (e.g., lab tests, scans) can be used for purposes of assessing study eligibility as long as all other requirements as stated in the protocol are met. For patients <18 years of age (or the legal minimum age in the relevant country) their legal guardian must give informed consent. Pediatric patients will be included in age-appropriate discussion in order to obtain verbal assent.

12. Male or Female. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    a. Male Participants:

    Male participants are eligible to participate if they agree to the following during the intervention period starting at the first dose of chemotherapy for at least 12 months after receiving the T-cell infusion, or 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 another 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.

b. Female Participants:

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

- Is not a WOCBP as defined in Section 2.3.1.

OR

- Is a WOCBP (as defined in Section 2.3.1) 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 2.3.1 during the intervention period 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. A 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 participant must be excluded from participation if the serum pregnancy result is positive.

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

2.2 Exclusion Criteria

1. **ALT** >2.5xULN without documented liver metastases/tumor infiltration.

   OR

2. **Total Bilirubin** >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
3. 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.
4. Clinically significant systemic illness (e.g. serious active infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the judgment of the PI would compromise the patient's ability to tolerate protocol therapy or significantly increase the risk of complications.
5. Untreated CNS metastasis. Extradural masses that have not invaded the brain parenchyma or parameningeal tumors without evidence for leptomeningeal spread will not render the patient ineligible. Patients with previous CNS tumor involvement that has been treated and is stable for at least 6 weeks are eligible.
6. Previous treatment with genetically engineered NY-ESO-1 specific T cells.
7. Uncontrolled intercurrent illness including, but not limited to:
   a) Clinically significant cardiac disease defined by congestive heart failure New York Heart Association (NYHA) Class >1.
   b) Uncontrolled clinically significant arrhythmia in last 6 months.
   c) Acute coronary syndrome (angina or myocardial infarction) in last 6 months.
   d) Severe aortic stenosis, symptomatic mitral stenosis.
8. Pregnant or breastfeeding females (due to risk to fetus or newborn).
9. 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).

10. Active HIV, HBV, HCV or HTLV 1 or 2 infection as defined below (due to increased risk of complications during the lymphodepleting regimen and confounding effects on the immune system):
    - 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 study treatment. For potent immunosuppressive agents, subjects with presence of hepatitis B core antibody (HBcAb) should also be excluded.
    - Active hepatitis C subjects as demonstrated by test for hepatitis C RNA. Subjects who are HCV antibody positive will be screened for HCV RNA by any RT PCR or bDNA assay. Eligibility will be determined based on a negative screening value.
    - Positive serology for HTLV 1 or 2.
11. Subject has history of active, chronic or recurrent (within the last year prior to enrolment) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments.

2.3 Prohibited Concomitant Medication and Treatment

Investigational anti-cancer therapies are prohibited on the study.

Following administration of cells, progression of disease should be confirmed prior to initiating any cancer directed therapy, including chemotherapy, immune therapy, radiation, or surgery.

The use of systemic steroids may abrogate the effects of the T cell therapy and therefore use is discouraged unless required to manage CRS (see Section 4.4 for CRS treatment recommendations) or other significant immune-mediated adverse events. According to local standard of care or ASCO guidelines (Smith 2015), steroids may be used as antiemetics with cyclophosphamide but must be discontinued no later than 24 hours prior to infusion of NY-ESO-1^{c259}T. Topical steroids for cutaneous application and inhaled steroidal treatments are permitted.

2.3.1 Contraception

NY-ESO-1^{c259}T may have adverse effects on a fetus in utero. Furthermore, it is not known if NY-ESO-1^{c259}T has 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.

Women in the following categories are not considered WOCBP

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

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

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range (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 Participants:

Male participants 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 WOCBP 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 Participants:

WOCBP 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. If randomized to Arm 2 WOCBP 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 (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods [b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] oral intravaginal transdermal injectable
Progestogen-only 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 participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. • Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. • Male condoms must be used in addition to hormonal contraception. 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 amenorrhoea 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, WOCBP must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 12 months after receiving T-cell infusion, or up to 4 months after there is no evidence of persistence/gene modified cells in the subjects' blood, whichever is longer. If there is any question that a WOCBP will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

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

2.4 Patient Enrollment

2.4.1 Screening

Patients that are identified by the Investigator as possible candidates for the trial must consent to screening activities that will first confirm that the patient is HLA and NY-ESO-1 positive prior to

conducting the remaining screening procedures as shown in the Schedule of Procedures in Appendix 2.

2.4.2 Screening Number

The screening period will begin on the day that the patient signs the Informed Consent. When the patient signs the Informed Consent, the patient will be assigned a screening number. Each site will be required to enter the patient information into the Electronic Data Capture (EDC) system and the EDC system will generate the screening number. Once assigned, a screening number cannot be used for another patient. If a screen failed patient later meets study eligibility and is re-screened, the patient will retain the original screening number.

2.4.3 Study Identification Number

After completion of all screening and baseline procedures and requirements for inclusion/exclusion are met, site personnel will complete the Subject Enrollment Form and send to the Sponsor for confirmation of eligibility prior to apheresis. Study procedures performed as part of standard of care prior to signing Informed Consent can be used for screening if they were performed within a medically reasonable period of time prior to signing the Informed Consent. There are no restrictions on the timing of HLA typing for screening and data can be taken from patients' records.

NOTE: The Study Identification Number will not be provided until the patient is assigned a screening number and registered in the EDC system. The Study Identification Number is a unique number assigned to each patient on the trial. A single patient cannot be assigned more than one Study Identification Number.

2.4.4 Screen Failures

A screen failure log documenting the investigators assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria should be maintained by the investigator, or tracked according to institutional guidelines.

2.5 Data Collection

All patients must have signed an Informed Consent Form and have filled out an eligibility checklist before entering the study. All toxicity and event data must be entered by the participating institution as stipulated in the Institutional contract with the Sponsor. In addition, complete records will be maintained on each patient at the participating institutions. These will consist of the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will serve as the primary source of material that forms the basis for the research record and will be available for monitoring purposes.

The Investigators at each site will be responsible for the collection, maintenance, and quality control of the study data. The Investigator at each site is responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes. The anonymity of participating subjects must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the regulatory authority, study monitor, or sponsor representatives. The Investigators will allow GSK, and/or the Competent Authority to inspect study documents (e.g. consent forms, drug distribution forms, IRB/IEC approval) and

pertinent hospital or clinical records for confirmation of data throughout the study period.

An EDC system will be used to collect data for Cohorts 2, 3 and 4. Trial data will be captured through an electronic Case Report Form (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. CRO).

The specifications for the EDC system will be documented and approved before the development is completed and the EDC system is released for live use. The validation of the eCRF data will be defined. 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 CFR21 Part 11 requirements. All users will access the system using their 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.

Medications and AEs will be coded using dictionaries specified by the Sponsor.

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

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

2.5.1 Source Documents

Source documents are original documents, data and records which include hospital records, clinic and office charts, laboratory data/information, patient diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays. The Investigators/Institutions will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections, providing direct access to source data documents.

2.5.2 Protocol Violations

Any protocol violations and/or deviations should be directly reported to the Sponsor and the appropriate documentation obtained. The Investigator will in turn report them to the institution's IRB/IEC.

3 Study Implementation

3.1 Study Design

This trial was originally designed as a single arm pilot study to determine whether T cells genetically engineered to recognize an HLA-A2 binding peptide from NY-ESO-1 induce antitumor responses in patients with synovial sarcoma. The goal of this pilot study was to assess whether this approach also induces a substantial rate of objective antitumor responses as a first step toward a larger randomized study of this therapy in synovial sarcoma using the same platform. Exploratory biologic studies are included to look for correlations between biologic endpoints and clinical response.

This trial expansion is based on favorable results from the single arm pilot study of Cohort 1 and will enroll additional patients into three cohorts designated as Cohorts 2, 3 and 4.

3.2 Treatment Plan

All eligible patients will be treated with lymphodepleting chemotherapy and NY-ESO-1^{c259}T. The final patient of Cohort 1 was treated on 15 June 2015. Newly enrolled patients will be allocated to subsequent available cohorts as eligible based on NY-ESO-1 expression and slot availability for each cohort. The Sponsor may choose to terminate the study at any point. All drugs administered will be open label. Cohorts 3 and 4 will accrue sequentially.

Patient characteristics and lymphodepleting chemotherapy for Cohorts 1, 2, 3 and 4 are described below. The dose of NY-ESO-1^{c259}T is described in Section 3.2.7. Patients may become eligible for a second infusion of NY-ESO-1^{c259}T, depending on allocated cohort and response to the first infusion, as defined in Section 3.5.3.

3.2.1 Cohort 1

Up to 20 patients with high tumor expression of NY-ESO-1 will be enrolled into Cohort 1 and will receive Regimen A as described in Section 3.3.3. High tumor NY-ESO-1 expression is defined as 2+ or 3+ by immunohistochemistry (IHC) in ≥ 50% cells. Enrollment into this cohort is now complete.

3.2.2 Cohort 2

Up to 15 patients with low tumor expression of NY-ESO-1 will be treated in Cohort 2 and receive Regimen A, as described in Section 3.3.3, and NY-ESO-1^{c259}T. Low tumor NY-ESO-1 expression is defined as ≥ 1+ by IHC in ≥ 1% cells but not to exceed 2+ or 3+ in ≥ 50% cells.

Stopping criteria for Cohort 2 are based on responses to treatment using Regimen A. Based on the observed response rate in Cohort 1 of 50% in the mITT population (see Section 6.2), if 0 or 1 responses are seen in the first 5 patients receiving Regimen A in Cohort 2 then the clinical effect will be reviewed in the context of the expression level to determine if the Cohort should close. If 3 or more responses are seen in the first 5 patients then the Cohort will recruit until completion. If 2 responses are observed in the first 5 patients, the Cohort will continue to enroll additional patients to further characterize the activity of the regimen. Refer to Section 6.3 for information on the rationale for stopping the cohort at this point.

Up to 5 additional patients considered unsuitable for Regimen A may also be enrolled in Cohort 2 and will receive Regimen C. Patients may be considered unsuitable for Regimen A for reasons that include, but are not limited to, advanced age, extent of prior therapies, or presence of co-morbidities. The assessment of whether a patient is suitable for Regimen A will be at the discretion of the Investigator.

3.2.3 Cohort 3

Up to 15 patients with high tumor expression of NY-ESO-1 will be enrolled into Cohort 3 to obtain at least 10 patients who receive Regimen B, as described in Section 3.3.3, and NY-ESO-1^{c259}T. High tumor NY-ESO-1 expression is defined as 2+ or 3+ by IHC in ≥ 50% cells.

Patients in Cohort 3 who do not experience an adequate response following Regimen B may be eligible for retreatment using Regimen A, as defined in Section 3.5.3

If 0 or 1 responses are seen in the first 5 patients in Cohort 3 then the clinical effect will be deemed insufficient to proceed with this approach and Cohort 3 will close due to inadequate activity. If 3 or more responses are seen in the first 5 patients in Cohort 3 then the Cohort will recruit until completion. If 2 responses are observed in the first 5 patients in Cohort 3, the Cohort will continue to enroll additional patients to further characterize the activity of the regimen. Refer to Section 6.3 for information on the rationale for stopping the cohort at this point. Enrollment into this cohort is now closed.

3.2.4 Cohort 4

On either completion of recruitment or closure of Cohort 3 up to 15 patients with high tumor expression of NY-ESO-1 will be treated in Cohort 4. Cohort 4 will receive Regimen C lymphodepletion, as described in Section 3.3.3, and NY-ESO-1^{c259}T. High tumor NY-ESO-1 expression is defined as 2+ or 3+ by IHC in ≥ 50% cells.

If 0 or 1 responses are seen in the first 5 patients in Cohort 4 then the clinical effect will be deemed insufficient to proceed with this approach and Cohort 4 will close due to inadequate activity. If 3 or more responses are seen in the first 5 patients then the Cohort will recruit until completion. If 2 responses are observed in the first 5 patients, the Cohort will continue to enroll additional patients to further characterize the activity of the regimen. The study may continue to enroll beyond 5 subjects based on clinical judgement to evaluate anti-tumor activity more comprehensively in the context of the totality of the data. Refer to Section 6.3 for information on the rationale for stopping the cohort at this point. If the anti-tumor activity with Regimen C is determined to be suboptimal, then future subjects enrolled in Cohort 4 will receive Regimen A.

3.2.5 Apheresis

A non-mobilized PBMC collection should be performed by apheresis at the enrolling institution according to the Hospital policies and procedures. Bilateral peripheral venous access should be used whenever possible but a temporary central venous catheter (CVC) may be placed for collection if peripheral venous access is inadequate. Standard clinical procedures for apheresis should be followed. Prior to apheresis, platelets should be >75 x10^9/L and hemoglobin >8.0 gm/dl. A large volume leukapheresis should be performed. For patients who are >50 kg, 10 to 15 liters should be processed per procedure; in patients ≤ 50kg, 2-3 blood-volumes should be processed per procedure with a goal of the procedure being collection of 1.0 x 10^8 PBMC/kg, and a minimum of 1.5x10^7 PBMC/kg. Prior to leukapheresis, an absolute lymphocyte count of ≥0.5 x 10^9/L and the CD3 count ≥200/μL is recommended. In cases where the minimum number of PBMC is not collected or the T cells cannot be administered (e.g. release criteria not met), a second apheresis may be performed. Citrate anticoagulant should be used. Prophylactic intravenous $CaCl_2$ and $MgSO_4$ infusions should be administered at the discretion of the apheresis physician.

3.2.6 T cell Transduction and Expansion

Leukapheresis product will be sent via designated express courier to a central manufacturer for transduction and expansion. Apheresis product will be labelled according to regulatory requirements and the Study Procedures Manual to ensure identification and traceability.

Current experience with NY-ESO-1^{c259}T is with total cell doses in the range of ~1 – 15×10^9 cells with a transduction level of ~20 – 75%. Thus, the target dose of 5×10^9 transduced cells with a minimum dose of 1×10^9 transduced cells and a maximum of 6 x 10^9 transduced cells is within a range that has been effective and safe for cell therapies (Section 3.2.7).

The final cell product, NY-ESO-1^{c259}T, is tested using pre-established release criteria. Expanded cells meeting the certificate of analysis will be cryopreserved then shipped back via designated express courier to the participating site where they will be thawed and infused on Day 0.

A Certificate of Analysis sample for the release criteria for the T cell product shown is in Table 1 below.

Table 1: Sample Certificate of Analysis Release Criteria

Test	Method	Criteria
Cell viability on sentinel tube	Trypan blue exclusion	≥70%
% CD3 positive T cells	Flow cytometry	≥80%
Endotoxin	(LAL Kinetic Method)	≤ 0.5 EU/mL
Mycoplasma	PCR	Negative
VSV-G DNA(RCL)	PCR	Negative
Transduction efficiency (NY-ESO-1 TCR)	Flow Cytometry Dextramer Positive	≥10%
Transduction efficiency (copy number)	PCR	0.1≤x≤5 average copies/cell
Bovine Serum Albumin (BSA)	ELISA	≤ 1 mcg/ml
Bacterial culture	Culture	No growth
Fungal culture	Culture	No growth

3.2.7 Cell Dose

Patients who are ≥40kg will receive the target cell dose of 5×10^9 transduced cells with a minimum 1×10^9 transduced cells and a maximum of 6×10^9 transduced cells. Patients <40 kg, however, will be dosed per body weight with a minimum 0.025×10^9 transduced cells/kg, and a target dose of 0.125×10^9 transduced cells/kg. For cohorts 2, 3 and 4, where at the end of manufacture there are insufficient transduced cells to meet the minimum required cell dose, additional NY-ESO-1^{c259}T will be manufactured using unused apheresis product. This will increase the likelihood that a patient enrolled onto a cohort is ultimately treated.

3.3 Drug Administration

Dosages of cyclophosphamide will be adjusted for obese patients and the dose of fludarabine for renal dysfunction as described below. Institutions are permitted to use their standard guidelines for administration, hydration, and monitoring parameters pertaining to chemotherapy agents

utilized in this protocol. In the absence of institutional standards, suggested guidelines are detailed below.

3.3.1 Timing

Apheresis and subsequent chemotherapy should be conducted following the required washout periods after the previous dose of treatment. Preceding anti-neoplastic treatment will need to be completed at an appropriate time prior to lymphodepleting chemotherapy (see Section 2.1)

Patients will initiate lymphodepleting therapy upon receipt by the Sponsor of satisfactory documentation of in-process testing demonstrating that the product has achieved release criteria (Table 1). In the unlikely event that lymphodepleting therapy has been initiated, but final cell product release criteria are not met, discussions between the manufacturing site, Principal Investigator, and Sponsor Study Physician will be conducted to evaluate the safety and feasibility of cell administration. The Competent Authority and IRB/IEC will be notified as necessary. Should the cell product be unable to be administered, the Investigator's clinical team will provide standard supportive care, e.g. G-CSF, and monitoring until full recovery.

3.3.2 Lymphodepleting Chemotherapy and Cell Infusion

Patients will begin infectious prophylaxis for pneumocystis carinii, herpes zoster and herpes simplex the day prior to commencing lymphodepletion, or as clinically indicated. Patients may be admitted to the hospital for chemotherapy administration. Chemotherapy conditioning may also be performed as an outpatient procedure at the discretion of the PI. Antiemetics and hydration for administration of chemotherapy will be given according to standard institutional practice.

3.3.3 Lymphodepleting Regimens

<table>
<tr><th colspan="5">Regimen A</th><th rowspan="2">Recommended supportive medication</th></tr>
<tr><th>Day</th><th>Drug</th><th>Dose</th><th>Route</th><th>Administration</th></tr>
<tr><td>-5</td><td>Fludarabine[1]</td><td>30 mg/m^2</td><td>IV</td><td>in 50 – 100ml (concentration of 1mg/mL or less) 0.9% NaCl over 30 mins*</td><td rowspan="10">Hydration: Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions
Mesna: may be given per institutional guidelines or as recommended in Section 3.4
Cell therapy premedication: premedication should be given approximately 30-60 minutes prior to the NY-ESO1^{c259}T infusion as described in Section 3.5.1
G-CSF: first dose on Day +2 or as described in Section 4.6.1</td></tr>
<tr><td>-4</td><td>Fludarabine[1]</td><td>30 mg/m^2</td><td>IV</td><td>in 50 – 100ml (concentration of 1mg/mL or less) 0.9% NaCl over 30 mins*</td></tr>
<tr><td rowspan="2">-3</td><td>Fludarabine[1]</td><td>30 mg/m^2</td><td>IV</td><td>in 50 – 100ml (concentration of 1mg/mL or less) 0.9% NaCl over 30 mins*</td></tr>
<tr><td>Cyclophosphamide[2]</td><td>1800 mg/m^2</td><td>IV</td><td>in 200 – 500 0.9% NaCl over 2 hours*</td></tr>
<tr><td rowspan="2">-2</td><td>Fludarabine[1]</td><td>30 mg/m^2</td><td>IV</td><td>in 50 – 100ml (concentration of 1mg/mL or less) 0.9% NaCl over 30 mins*</td></tr>
<tr><td>Cyclophosphamide[2]</td><td>1800 mg/m^2</td><td>IV</td><td>in 200 – 500 0.9% NaCl over 2 hours*</td></tr>
<tr><td>-1</td><td colspan="4"></td></tr>
<tr><td>0</td><td colspan="4">NY-ESO1^{c259}T infusion[3]</td></tr>
</table>

+1		
+2	start **G-CSF**[4]	

Notes:

1 Fludarabine dose will be adjusted in renal impairment as described in Section 3.3.4
2 Cyclophosphamide dose will be adjusted in obese patients as described in Section 3.3.5
3 Administration of NY-ESO1^{c259}T infusion is described in Section 3.5
4 Pegylated G-CSF may be given instead of short acting G-CSF according to institutional standard practice. Recommendations for G-CSF administration are listed in Section 4.6.1.

* Or per institutional standards

Regimen B					**Recommended supportive medication**
Day	**Drug**	**Dose**	**Route**	**Administration**	**Hydration:** Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions **Mesna:** may be given per institutional guidelines or as recommended in Section 3.4 **Cell therapy premedication:** premedication should be given approximately 30-60 minutes prior to the NY-ESO1^{c259}T infusion as described in Section 3.5.1 **G-CSF:** first dose on Day +2 or as described in Section 4
-5					
-4					
-3	**Cyclophosphamide**[1]	1800 mg/m^2	IV	in 200 – 500 0.9% NaCl over 2 hours*	
-2	**Cyclophosphamide**[1]	1800 mg/m^2	IV	in 200 – 500 0.9% NaCl over 2 hours*	
-1					
0	**NY-ESO1^{c259}T infusion**[2]				
+1					
+2	start **G-CSF**[3]				

Notes:

1 Cyclophosphamide dose will be adjusted in obese patients as described in Section 3.3.5
2 Administration of NY-ESO1^{c259}T infusion is described in Section 3.5
3 Pegylated G-CSF may be given instead of short acting G-CSF according to institutional standard practice. Recommendations for G-CSF administration are listed in Section 4

* Or per institutional standards

Regimen C					**Recommended supportive medication**
Day	**Drug**	**Dose**	**Route**	**Administration**	**Hydration:** Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions **Mesna:** may be given per institutional guidelines or as recommended in Section 3.4 **G-CSF:** given as 24 hours post the final dose of cyclophosphamide or as described in Section 4
-7	**Fludarabine**[1]	30 mg/m^2	IV	in 50 – 100ml (concentration of 1mg/mL or less) 0.9% NaCl over 30 mins*	
	Cyclophosphamide[2]	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 30 mins*	
-6	**Fludarabine**[1]	30 mg/m^2	IV	in 50 – 100ml (concentration of 1mg/mL or less) 0.9% NaCl over 30 mins*	

	Cyclophosphamide[2]	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 30 mins*	**Cell therapy premedication:** premedication should be given approximately 30-60 minutes prior to the NY-ESO1^{c259}T infusion as described in Section 3.5.1
-5	**Fludarabine**[1]	30 mg/m^2	IV	in 50 – 100ml (concentration of 1mg/mL or less) 0.9% NaCl over 30 mins*	
	Cyclophosphamide[2]	600 mg/m^2	IV	in 100 – 250 ml 0.9% NaCl over 30 mins*	
-4	start **G-CSF**[3]				
-3					
-2					
-1					
0	**NY-ESO1^{c259}T infusion**[4]				

Notes:

1 Fludarabine dose will be adjusted in renal impairment as described in Section 3.3.4
2 Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice. Recommendations for G-CSF administration are listed in Section 4
3 Administration of NY-ESO1^{c259}T infusion is described in Section 3.5

* Or per institutional standards

3.3.4 Dose Adjustments for Fludarabine

Dose of fludarabine will be adjusted for patients with renal dysfunction as follows:

Creatinine clearance	**Fludarabine dose**
≥80 mL/min	30 mg/m^2
40 – 79 mL/min	20 mg/m^2

3.3.5 Dose Adjustments for Cyclophosphamide

If the subject's weight is greater than 175% Ideal Body Weight (IBW) then calculate cyclophosphamide dose based on Adjusted Body Weight (ABW).

No dose adjustments will be made for obese subjects receiving 600 mg/m^2 because the adjustment is not necessary with the lower dose of cyclophosphamide.

3.3.5.1 Calculating Ideal Body Weight

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

3.3.5.2 Calculating Adjusted Body Weight

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

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

The IBW and ABW are used to calculate medication dosages when the patient is obese. This formula only applies to persons 152 cm or taller.

3.3.5.3 Cyclophosphamide Dose Adjustment for Pediatric Subjects

For pediatric subjects, where subject weight is >175% of the calculated IBW use the following formula to calculate cyclophosphamide dose:

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

3.4 Mesna Administration

Mesna will be given to cover the duration of cyclophosphamide chemotherapy according to local practice. The London Cancer 2014 guideline for high dose cyclophosphamide is provided as an example and recommends:

(50% cyclophosphamide dose) as an IV bolus pre infusion, 3hr, 6hr and 9-hr post on each day of cyclophosphamide administration.

Regimen	Mesna dose	%age Cy dose	Dose schedule
A	900 mg/m^2	50%	0hr, 3hr, 6hr, 9hr on each day of Cy administration
B	900 mg/m^2	50%	0hr, 3hr, 6hr, 9hr on each day of Cy administration
C	120 mg/m^2	20%	0hr, 3hr, 6hr, 9hr on each day of Cy administration

http://www.londoncancer.org/media/75898/140214-London-Cancer-Mesna-Guideline-v1.pdf

3.5 NY-ESO-1^{c259}T Cell Administration

On Day 0, the subject will receive thawed NY-ESO-1^{c259}T by intravenous infusion. The infusion bag will be labeled according to applicable regulatory requirements including batch number, protocol number, number of transduced cells and the subject's study identification number. Prior to infusion, two clinical personnel will independently verify all the information in the presence of the subject and to confirm that the information is correctly matched to the subject, as per institutional blood bank procedures.

3.5.1 Premedication

Subjects will be premedicated with antihistamines and acetaminophen according to institutional practice 30-60 minutes prior to cell infusion. Steroids must not be given as premedication.

3.5.2 Cell Infusion

NY-ESO-1^{c259}T must not be thawed until immediately prior to infusion. The cells can be thawed either in a water bath at the patient's bedside or in a centralized facility, according to institutional standard procedures. The cells must be infused without delay and, if thawed centrally, must be transported to the patient by appropriately trained clinical staff, to preserve the chain of custody. The cell product must not be washed or otherwise processed. It is expected that the infusion will

commence within approximately 10 minutes of thawing and complete within 45 minutes of thawing to minimize exposure of the cell product to cryoprotectant. If the cells are provided in multiple bags, the second bag must not be thawed until half the first has been infused without reaction.

If after thawing the inner infusion bag is damaged or leaking, the PI and Sponsor should be notified and the cells should not be infused.

NY-ESO-1^{c259}T will be administered using a dual spike infusion set by gravity over 15-45 minutes in the absence of reaction. It is recommended that the cells are infused without a filter, however if a filter is required by institutional practice the pore size must not be smaller than 170 μm. Infusion pumps must not be used. For administration of the cells, 100 - 250 ml of 0.9% sodium chloride should be connected to the second lumen of the infusion set, used to prime the line, and then the lumen closed. On completion of the infusion of a bag of NY-ESO-1^{c259}T, the main line should be closed and approximately 50ml saline transferred into the cell bag, and then infused to minimize the loss of cells. This process should be repeated for each cell bag if multiple bags are provided. On completion of the cell infusion the set should be flushed using additional saline from the attached bag.

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.

The day of T cell infusion may be delayed in patients with significant complications of chemotherapy if according to the Investigator it is in the best interest of the patient. The timing of all assessments post-infusion will be calculated with reference to the T-cell infusion date. Subjects who have undergone leukapheresis but do not receive the T-cell infusion will be replaced. Cytopenias alone should not be a reason to delay T-cell infusion unless complications are present.

3.5.3 Second T Cell Infusions

Second infusions can occur in two settings:

1. Patients enrolled onto any cohort who have a confirmed response, or have stable disease for >3 months, then progress, are eligible for a second infusion of NY-ESO-1^{c259}T. Patients with confirmed responses or stable disease that qualify for a second infusion will receive lymphodepleting chemotherapy and T cell infusion as received for the first infusion. A second infusion of NY-ESO-1^{c259}T may only be given to these patients if their tumors continue to express the appropriate antigen target. Eligible patients must provide fresh tumor biopsies at confirmation of progression of disease. The biopsy collected at the time of progression is required for determination of NY-ESO-1 positivity prior to a second infusion.
2. Patients in Cohort 3 and 4 who have progressive disease or stable disease ≤3 months as best response, may receive a 2nd treatment of NY-ESO-1^{c259}T using the Regimen A lymphodepletion to determine if more intense lymphodepletion can result in an improved best response. Biopsies are not required for retreatment of these patients. It is assumed that the antigen expression would not have changed, whereas a patient who responded and progressed may have progressed due to loss of antigen.

Where available, previously manufactured cell product will be used; otherwise any residual apheresis product from collections prior to receipt of the gene modified T cells will be utilized for a new product manufacture. Patients will not be re-apheresed for cells unless there are no gene modified cells detectable by QPCR and approval to do so has been received by the Safety Monitoring Team consisting of the Sponsor and Investigators prior to the procedure.

Patients may receive a maximum of two treatments with NY-ESO-1^{c259}T. The second cycle (i.e. re-treatment) can be given no sooner than 60 Days from the first infusion and no later than 2 years after the first infusion. Decisions to retreat with a second infusion will be discussed with the Sponsor and Investigators.

3.5.3.1 Additional Eligibility Criteria (Prior to Second T-Cell Infusion)

Prior to receipt of a second infusion of NY-ESO-1^{c259}T, all patients must remain eligible to receive manufactured T-cell product as defined in Section 2.1 and Section 2.2 and meet the following inclusion criteria:

1. Patient has had a documented confirmed response (PR or CR) or stable disease >3 months followed by confirmed PD after the first T-cell infusion. In addition, patients in Cohort 3 and 4 who have progressive disease or stable disease ≤3 months as best response may be eligible for second infusion (see Section 3.5.3).
2. A second T cell infusion is recommended by the Investigator.
3. Patients in any cohort with a confirmed response (PR or CR) or stable disease must have a new tumor biopsy confirming NY-ESO-1 expression by immunohistochemistry.
4. Patient has voluntarily agreed to receive a second T-cell infusion by giving written informed consent.
5. Patient has toxicity from first T-cell infusion that resolved to Grade ≤1.
6. Manufactured T-cell product must be available.
    - In cases where previously manufactured T-cell product is not available, any residual leukapheresis product from collections prior to receipt of the gene modified T cells will be utilized for a new product manufacture.
    - In cases where residual leukapheresed product is not available, patients can agree to be re-leukapheresed for cells only in circumstances where there are no detectable gene modified cells.

Furthermore and prior to receipt of a second T-cell infusion, a patient meeting the following criterion is not eligible for a second T-cell infusion:

7. Patient with any Grade 4 CRS or clinically life-threatening (Grade 4) AEs deemed at least possibly related to the NY-ESO-1c259T cell product by the principal investigator and study sponsor reported during the first T-cell infusion.

3.6 Safety Considerations

3.6.1 Early Stopping Rule

Throughout the conduct of the study, safety data will be reviewed for each subject on an ongoing basis. Additionally, periodic safety reviews will be undertaken by the Sponsor.

If the following events occur, further enrolment to the study will be suspended and the regulatory authorities informed.

Any death occurs that is deemed to be probably or definitely related to the investigational medication/cell product by the principal investigator and study sponsor;

Or

Two (2) or more grade 4 autoimmune events deemed probably or definitely related to the investigational medication/cell product by the principal investigator and study sponsor;

Or

An apheresis confirmed positive biological replication competent lentivirus (RCL) occurs (see Section 3.9.4) or confirmed positive peripheral blood mononuclear cell (PBMC) RCL and no other vector lot is available

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

3.7 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 8.3 and Section 8.4) 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 Appendix 2).

3.8 On-Study Protocol Evaluations

3.8.1 Screening Studies

Note: to be performed ≤7 days prior to apheresis, unless otherwise stated

- Disease staging evaluation (CT or MRI within one month of apheresis)
- History and complete physical examination, including height, weight, ECOG/Lansky and vital signs.
- HLA screening (any time prior to apheresis)
- NY-ESO-1 screening (any time prior to apheresis)
- Labs: hematology, PT, PTT, chemistry (includes LDH, SGPT (ALT), SGOT (AST), alkaline phosphatase, bilirubin (total and direct), BUN/urea, creatinine, electrolytes, calcium, magnesium, phosphate, albumin),
- Urine or serum pregnancy test: required for females of childbearing potential
- Urinalysis
- Infectious disease markers: HIV, HBV, HCV, HTLV 1+2, CMV, EBV, and syphilis (spirochaete bacterium) (within one month prior to apheresis)
- 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.
- ECG.

3.8.2 Baseline Studies

Note: to be performed within 7 days prior to initiating chemotherapy, unless otherwise stated

- Disease staging evaluation (CT or MRI)
- History and complete physical examination, including height, weight, ECOG/Lansky and vital signs.
- Labs: hematology, PT, PTT, chemistry (includes LDH, SGPT (ALT), SGOT (AST), alkaline phosphatase, bilirubin (total and direct), BUN/urea, creatinine, electrolytes, calcium, magnesium, phosphate, albumin), uric acid, CRP, amylase, lipase, ferritin, rheumatoid factor, ANA, thyroid function.
- Blood CMV DNA PCR
- RCL
- Urinalysis
- Patients ≥65 yrs 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.

  Note: Estimates of creatinine clearance decrease in accuracy with increasing subject age, tending to underestimate renal function in older patients (Raj 2006). Accurate information on renal function is needed to evaluate eligibility for the study and to determine chemotherapy dose, therefore older patients will have renal function measured by the above methods to ensure accuracy.
- Urine or serum pregnancy test: required for females of childbearing potential.
- ECG
- 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 [TCR] infusion.
- Reports of cardiac events in subjects with cardiac or pericardial masses following treatment with NY-ESO-1c259T will continue to be monitored through normal proactive Pharmacovigilance.
- Re-screening for infectious disease markers is not required at baseline (prior to lymphodepletion)

Note: Patients must meet eligibility criteria identified in Section 2 for those tests repeated at re-staging (Baseline) prior to T cell infusion (see Appendix 2).

3.8.3 Baseline Research Studies

- Serum cytokine levels
- Persistence/Expansion of NY-ESO-1 specific T cells
- Flow cytometry (includes lymphocyte subset phenotyping, including Tregs)
- Tumor biopsy: when possible, patients with safely accessible tumor will be asked to undergo core needle tumor biopsies

3.8.4 Monitoring During Chemotherapy (Daily from first day of chemotherapy)

- Daily laboratory evaluation: hematology, chemistry (includes LDH, SGPT (ALT), SGOT (AST), alkaline phosphatase, bilirubin (total and direct), BUN/urea, creatinine, electrolytes, calcium, magnesium, phosphate, uric acid, albumin, CRP)

  Note: institutions must follow their local procedures for clinical care of patients receiving cyclophosphamide and/or fludarabine

3.8.5 Day 0: Clinical Monitoring During and After Cell Infusion

- Symptom-directed physical examination prior to cell infusion
- Monitoring will include vital signs and oxygen saturation prior to and approximately every 15 minutes until one hour after completion of infusion or until stable for two consecutive measures, whichever is later. Once stable, vital signs will be monitored routinely

  Note: Supplemental oxygen should be available at the bedside
- If an allergic or other acute reaction occurs, studies appropriate for investigation of a transfusion reaction will be performed (urinalysis, hematology, Coomb's test)
- Clinical labs:

  Hematology, chemistry, (includes LDH, SGPT (ALT), SGOT (AST), alkaline phosphatase, bilirubin (total and direct), BUN/urea, creatinine, electrolytes, calcium, magnesium, phosphate, CRP, uric acid, albumin)
- CMV PCR
- Research studies:

  Serum cytokine levels

3.8.6 Monitoring Day 1 to Week 4

Note: days 1, 3, 4, 7 time-points may be performed ± 1 days

- Physical exam: Day 1, 3, 4 and 7 obtain on at least 3 separate days. From Day 8 to Week 4, perform once weekly
- Hematology: days 1, 3, 4 and 7 obtain on at least 3 separate days. From Day 8 to Week 4, obtain once weekly
- Chemistry (includes LDH, SGPT (ALT), SGOT (AST), alkaline phosphatase, bilirubin (total and direct), BUN/urea, creatinine, electrolytes, calcium, magnesium, phosphate, LDH, CRP, uric acid and albumin. Day 1, 3, 4 and 7. From Day 8 to Week 4, obtain once weekly
- CMV PCR: Week 2 and 4
- Radiographic imaging for response assessment at Week 4 (may be performed ± 4 days)
- Research Studies:

  Serum Cytokine Levels: days 1, 4 and weekly to Week 4

Persistence/Expansion of NY-ESO-1 specific T cells: days 4, 7, Week 2, Week 4

Flow cytometry (includes lymphocyte subset phenotyping including Tregs) day 7 and Week 4

3.8.7 On Treatment Evaluations After Week 4

Note: Evaluations from Week 4 through Month 6 may be performed ± 1 week; for visits >9 months, evaluations may be performed ± 3 weeks

- Radiographic imaging for response assessment with restaging: Week 8, Week 12, Month 6, Month 9 and Month 12, then every 3 months for 2 years and then yearly until 5 years post-infusion.
- Evaluations at Week 6, Week 8, Week 12, Month 4, Month 5, Month 6, Month 9, Month 12, then every 3 months until 2 years post-infusion, then every 6 months until 5 years post-infusion or until progression and at discontinuation will include the following (unless otherwise stated):

  Physical examination, including vital signs. Hematology, chemistry (electrolytes/ liver/ renal function)
- Additional visits for hematology tests only (physical examination and review not required): Week 5, Week 10
- CMV PCR: Week 6 and 8
- Detection of RCL as described in Section 3.9.5 and Appendix 2
- Research studies (Refer to Appendix 2):

  Serum cytokine levels (Week 6, Week 8)

  Persistence/expansion of NY-ESO-1 specific T cells: if the patient is in the interventional phase of the study, samples are collected at Week 8, Week 12, Month 12 and every 6 months until 5 years post-infusion as per Appendix 2. If the patient is in LTFU, samples for persistence are collected as per Appendix 4

  Flow cytometry (Note: draw only when patient's absolute leukocyte count (ALC) is $\geq 0.2 \times 10^9$/L) Week 8, Months 6, 12 and every 3 months until 2 years post-infusion, then every 6 months until 5 years post-infusion

  Tissue biopsy at Month 2 and if possible at disease progression (see section 3.9)

3.9 Biologic studies

3.9.1 Monitoring Persistence/Expansion of NY-ESO-1^{c259}T

The goal of the immune/biologic studies are to monitor the expansion/persistence of the adoptively transferred cells to test the hypothesis that clinical response correlates with the 1) degree of expansion and/or 2) persistence of the genetically modified cell *in vivo*.

Due to nature of this study, it is possible that expansion of specific T-cell clones will be observed as tumor reactive T-cells proliferate. Therefore, care will be taken to track NY-ESO-1^{c259}T persistence. Genetically modified cells will be measured in blood samples collected periodically

according to the schedule in Appendix 2. Persistence of genetically modified cells will be measured using PCR to transgene specific sequences. Additionally for specific cutoff values such as transduction efficiency of the infused product (which requires 10% NY-ESO-1 reactive T cells) the value obtained with antibodies to the BV13.1 chain of the T cell receptor will be used.

In addition to correlating persistence with response outcomes, monitoring persistence is important due to the theoretical risk of insertional mutagenesis in cells transduced with a lentiviral vector. While this risk has been realized in stem cell gene transfer studies, T cells appear resistant to transformation by integrating viruses (Cattoglio 2010; Newrzela 2008). Monitoring for insertional oncogenesis follows the recommendations set forth in the FDA guidance (Guidance for Industry, Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events 2006; EMA CHMP Guideline on follow-up of patients administered with gene therapy medicinal products 2009).

Peripheral blood mononuclear cells (PBMCs) samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in patients at baseline, 3, 6, and 12 months post-infusion, every 6 months until 5 years post-infusion and every year until 15 years post infusion. The samples will be tested 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 WPRE or Psi DNA copies reflects persistence of the transduced T cells. If at 1 year or beyond post-infusion greater than 1% PBMCs test positive for vector sequences, then the patient's PBMCs will be evaluated for integration site analysis (see below). If no gene modified cells are detected for three consecutive assessments and subject is 5 years post-infusion, no further monitoring of PBMCs is required and collection of samples for persistence may be stopped and the subject can be followed remotely for up to a total of 15 years post infusion. Note that samples will still need to be collected until year 15 for RCL as described in Section 3.9.5.

If persistence, as detected by the presence of vector sequences (WPRE or Psi DNA copies), is present in >1% of PBMC at 1 year or beyond post-infusion, DNA from the patient's PBMCs will be sent for integration site analysis.

If there is clonal dominance (either monoclonality or oligoclonality) the integration site analysis will be repeated within 3 months on a new sample. If the retest demonstrates the same dominant clones, 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 regulatory agencies of the findings. If the integration site analysis indicates polyclonality of gene modified T cell population, then screening continues as scheduled.

3.9.2 Monitoring Treg Depletion

In addition to studies on the expansion and persistence of genetically engineered T cells, we will also monitor for Treg populations using antibodies to FOXP3+ cells. In this study, we will descriptively evaluate the relationship between FOXP3+ cells and tumor response.

3.9.3 Flow Cytometry

Flow cytometry will be conducted at a central laboratory designated by the Sponsor. (See Appendix 2)

3.9.4 Monitoring and Management of Replication-Competent Lentivirus

Replication Competent Lentivirus (RCL) is a theoretical risk associated with the use of lentiviral vectors; no RCL has ever been 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). RCR resulted in the onset of lymphoma in 3/10 monkeys after receiving cells transduced with an RCR contaminated vector lot (Donahue 1992). Updated γ retroviral packaging systems have not been associated with RCR, however as a result of the Donahue study, RCR/L must continue to be rigorously evaluated in vector and cell lots, and in subjects post infusion with any product involving a retrovirus (FDA 2000).

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 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 virus, or could increase the replication rate or pathogenicity of the subject's 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.

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject (FDA 2000). However, because the probability and characteristics of an RCL are unknown, no concrete plans have been put in place. Nevertheless, all agree that the subject must be isolated until an understanding of how to manage the subject becomes clear.

Approaches that have been discussed for managing the subject are the following:

- 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 and NIH.
- Inform local public health officials and CDC.
- Identify sexual partners and provide appropriate counseling and intervention.

3.9.5 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:

- cell product, whereby RCL testing will be performed by or under the direction of the manufacturing facility responsible for the manufacturing and release of the vector

- patient PBMCs which 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 and archived for up to 15 years post infusion; however, if VSV-G DNA copies are detected at any time point during the first 12 months after infusion, then patient samples will be tested until lentiviral gene copies are no longer detected in the subject.

3.9.6 RCL Safety Monitoring - Results

If a positive VSV-G DNA signal is obtained, following review by the Sponsor, the study PI will be informed and the subject scheduled as soon as possible for a retest and within one month after the initial positive result was reported to the Sponsor.

If the second test is positive, infusions for all subjects receiving 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 measuring replication and infectivity of viral particles will be performed on the leukapheresis product.

If the biological RCL test is positive, all infusions using the vector lot will be stopped. If the test is negative, infusions for all subjects can resume.

3.9.7 Blood Volume Restrictions for Research Samples:

Blood sample volume for the research purposes of this study will be restricted. The amount of blood drawn from adults (those 18 years of age or older, or relative country-specific guidelines) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, in an 8 week period. The amount of blood drawn for research purposes from pediatric patient subjects (those under 18 years of age or relative country-specific guidelines) will not exceed 5 mL/kg in a single day, and no more than 9.5 mL/kg over an 8 week period.

In the event that blood draws are limited due to these restrictions, research studies will be performed in order of priority in discussion with the Investigator and Sponsor.

3.10 Tumor Biopsy for Research

The assessment of biopsy material is essential for the development of the NY-ESO-1^{c259}T product; the information learned will build understanding of tumor immune escape mechanisms, as well as the ability of the cell product to induce or recover a broader anti-tumor immune response within each patient. Correlating this data with patient responses will be essential to understanding the mechanism of action of the NY-ESO-1^{c259}T product and mechanism(s) of tumor escape. The data will support late phase clinical development and in parallel will inform potential improvements that could be made to NY-ESO-1^{c259}T to enhance response and durability.

3.10.1 Tumor Biopsy at Baseline, Month 2, and Disease Progression

When possible, patients with safely accessible tumor will be asked to undergo core needle tumor biopsies at baseline and Month 2 (the biopsy may be taken ±4 weeks of the Month 2 visit). If possible, biopsies should consist of multiple cores taken from more than one lesion. Since lung lesions are common in synovial sarcoma and may not be amenable to core needle biopsy, fine needle aspirates from one lesion may be obtained based on interventional radiology recommendations. The baseline biopsy material may be collected anytime between two months

and 2 weeks (±1 week) prior to the start of chemotherapy, with a preference for the biopsy to be taken closer to the chemotherapy. The tumor tissue should be taken from non-target lesions, or from target lesions provided they are greater than 2cm. When possible the same lesion(s) should be biopsied at both baseline and Month 2. If it is not possible to biopsy the same non-target lesion(s) at Month 2, then (an) other non-target lesion(s) preferably in the same anatomical region should be biopsied. The apparent clinical or scan status of the lesion(s) biopsied at Month 2 should be noted at the time (e.g. decreased, stable, increased size or activity).

Patient will not be excluded from the study if tumor is not safely accessible or if patient does not opt for biopsy.

The investigational plan for the biopsies and the collection and sample preparation methods can be found in the Study Procedures Manual.

If feasible, biopsy material should also be collected when disease progression has been confirmed and documented, ideally on lesions that have progressed. If progression is identified in the same lesion(s) biopsied at Month 2, then this lesion would be preferred for repeat biopsy. A biopsy may be obtained any time post-progression during resection, if possible.

As stated in section 2.3, patients should not receive anticancer therapy, including surgical resections, prior to disease progression. In the event that a resection of target or non-target lesions is performed for disease progression, or prior to progression for medically justified reasons, a portion of the tissue must be made available to GSK for translational research studies to understand mechanisms of response or resistance to the therapy.

In patients who have an accumulation of pleural effusion, if there is a clinical requirement for removal of the effusion fluid at any time on study we request that samples be collected for GSK for translational research studies. If available, pleural effusion fluid should be collected in addition to and not in place of the requested tumor biopsies. We request that every attempt is made to collect both tumor biopsies and effusion fluid when it is possible and for each of the requested on-study time points.

3.11 Criteria for Completion of Interventional Phase, Transition to Long-Term Follow-up or Discontinuation

3.11.1 Interventional Phase:

All patients who receive one or more infusions of genetically engineered T cells will be followed as per Appendix 2 until they complete the interventional phase for one or more of the following events:

- If patient does not meet eligibility for additional cell therapy cycles(s) or had unacceptable toxicity precluding additional cell therapy cycle(s), AND develops progressive disease that requires treatment with tumor directed therapy.
- if they are unable to comply with study requirements, or
- Patient, parent or guardian choice (elective withdrawal).

The tests and procedures at discontinuation described in Appendix 3 should be performed, if possible, at the time a patient comes off regular study assessments, prior to entering long term

follow up, regardless of the reason, unless the test or procedure has been performed in the last 4 weeks (2 weeks for physical examination and laboratory assessment).

Subjects who remain progression free will continue to be assessed under the interventional phase of the protocol until 2 years post infusion as described in Appendix 2. After 2 years post the last T cell infusion all patients will transfer to the long term follow up schedule. Subjects who receive a second T cell infusion will be followed for 6 months post infusion as described in Appendix 2 before transferring to the long term follow up schedule.

3.11.2 Long-Term Follow-Up

All subjects will be followed for 15 years from the time of their last T cell infusion for observation of delayed adverse events in accordance with regulatory guidance.

If a subject receives a second T cell infusion, observation for long-term follow up restarts with the second infusion, and subjects will be followed for 15 years from the time of second T cell infusion. All subjects will continue to be followed for overall survival during the Long Term Follow Up (LTFU). LTFU will occur either as part of this study, or subjects will be rolled-over into a separate LTFU protocol (GSK208750 [ADP-0000-002]) when available. The LTFU protocol will undergo regulatory, institutional and ethics committee approval and subjects will be consented to this specific LTFU study for continued collection of LTFU data. Please refer to Appendix 4 for LTFU assessments.

Subjects who have progressive disease prior to one year will be assessed at 3 months for required persistence, RCL, hematology, chemistry, and physical exam but then should be monitored every 6 months post cell infusion until the end of year 5 post T cell infusion as described in Appendix 4.

The physical exam (including concomitant medications and adverse events) will be conducted with careful attention to features possibly related to oncoretroviral diseases including: (1) New malignancies, (2) New incidence or exacerbation of a pre-existing neurologic disorder, (3) New incidence of exacerbation of a prior rheumatologic or other autoimmune disorder, and (4) New incidence of a hematologic disorder. (5) Unexpected illness and hospitalization deemed related to gene therapy.

From year 6 to 15, subjects will be asked to return for testing only if vector modified cells were detected in the previous visit. If so, then blood for persistence of vector modified cells will be performed and an annual RCL testing (archive) collected. If no vector modified cells were detected in the previous visit, annual follow-up will be conducted by means of a clinical questionnaire completed via phone or through the mail by the study coordinator. A draft letter to the patient and the patient's primary doctor (if different than the study Investigator listed on this protocol) is provided in Appendix 5.

For as long as female patients have detectable gene modified cells, they will be advised to avoid pregnancy. Persistence data will be performed in real time and this data will be used to properly advise patients in a timely manner.

4 Supportive Care

4.1 Infection

Patients should receive prophylaxis against Pneumocystis pneumonia, herpes simplex, and varicella zoster and according to the hospital guidelines for at least 1 year after completing this therapy. In addition, measures to treat and prevent infection may be provided in accordance with hospital guidelines. In particular, fever and neutropenia should be aggressively managed as well as preemptive influenza therapy and other standard therapies for immunocompromised hosts.

4.1.1 Cytomegalovirus

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. CMV IgG positive subjects should be measured at baseline and monitored 2-weekly for CMV viremia by CMV DNA PCR from the start of lymphodepletion until 8 weeks post infusion of NY-ESO-1^{c259}T as shown in Appendix 2. In the event CMV viremia is observed a specialist in infectious disease should be consulted and treatment initiated if necessary according to institutional practice.

If a subject experiences prolonged or recurrent 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 4.6.2.

4.1.2 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 lymphodepleting chemotherapy.

4.2 Hematologic and Blood Product Support

Blood product support should be provided to maintain platelets > 10 x10^9/L, Hb > 8.0 g/dL and as clinically indicated (AABB guideline, Kaufman 2015).

4.2.1 Blood Product Irradiation

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 conditioning chemotherapy and following conditioning chemotherapy until at least 6 months following study T cell infusion or until lymphocyte count returns to ≥1.0 x10^9/L (whichever is longer) must be irradiated. Patients who have received fludarabine as part of the conditioning chemotherapy must continue to receive irradiated blood products for at least 6 months post study treatment. Patients receiving steroids or other immunosuppressive therapies should also receive irradiated blood products regardless of above time intervals.

4.2.2 CMV 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 should receive leukoreduced blood products where possible (excluding the study T cell infusion). Where leukoreduced blood is not available, CMV negative

patients must only receive blood products from CMV-seronegative donors from study entry to study discontinuation.

4.3 Treatment of Autoimmunity

Patients 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 T cell therapy. If the patient sustains persistent Grade 2, or Grade 3 or 4 autoimmunity, consideration should be given to administration corticosteroid therapy, either topically (e.g. skin, eyes) or systemically, as clinically indicated.

4.4 Treatment of Cytokine Release Syndrome

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 2014).

Table 3 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 typical of CRS are listed in the table below according to severity. 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 as well CRP and Ferritin levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

Table 2 Management Guidelines for Cytokine Release Syndrome

Grade	Clinical Presentation for Grading Assessment	Management Guidelines
1	Constitutional symptoms not life-threatening (e.g., fever, nausea, fatigue, headache, myalgias, malaise)	• Vigilant supportive care[1] • Assess for infection and treat[2]
2	Symptoms require and respond to moderate intervention (Hypotension responds to fluids or	• Monitor cardiac and other organ function • Vigilant supportive care[1].

	one low dose pressor, hypoxia responds to <40% O_2, and/or Grade 2 organ toxicity)	• Assess for infection and treat[2] • Treat hypotension with fluid and pressors. • Administer O_2 for hypoxia. • Administer tocilizumab ± corticosteroids[3] in subjects with extensive co-morbidities or of older age.
3	Symptoms require and respond to aggressive intervention hypotension requires multiple pressors or high dose pressors hypoxia requires ≥40% O_2 Grade 3 organ toxicity or Grade 4 transaminitis	• Monitor subject very closely for cardiac and other organ dysfunction. Most likely will require monitoring in an intensive care unit (ICU). • Vigilant supportive care[1] • Assess for infection and treat[2] • Treat hypotension with fluid and pressors. Administer O_2 for hypoxia. • Administer tocilizumab ± corticosteroids[3]
4	Life-threatening symptoms Grade 4 organ toxicity (excluding transaminitis)	• Manage subject in ICU • Intensive supportive care including mechanical ventilation, fluids, pressors, antibiotics and other measures as required • Administer tocilizumab ± corticosteroids[3]
5	Death	

1. Supportive care includes: monitor fluid balance, maintain adequate hydration and blood pressure
2. 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.
3. Other immunosuppressive agents may be used, including TNFα and IL-1R inhibitors

Source: Lee 2014

Subjects requiring immunosuppressive intervention may receive tocilizumab, steroids, or both (Davila 2014; Lee 2014). 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., recommend administration of tocilizumab 4 mg/kg administered over 1 hour in adult subjects as the first-line treatment of severe CRS (Lee 2014). 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).

Subjects unresponsive to tocilizumab or experiencing severe neurological symptoms (e.g. confusion, delirium, seizure, etc.) may require treatment with steroids. Lee et al., recommend steroids as second-line therapy for CRS as the response to tocilizumab may be more rapid and owing to the potential of steroids to attenuate the anti-tumor effects of the adoptive T-cell therapy. 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 cytokine release syndrome 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 review to the most recent version of the product label for tocilizumab.

4.5 Monitoring and management for Demyelinating Neuropathy and other Neurological events

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

4.6 Management of Graft-versus-Host Disease

Autologous graft-versus-host disease (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 autologous stem cell transplant (ASCT) in patients with multiple myeloma. There is the potential for subjects who receive cytoreductive 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).

4.6.1 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 lymphodepleting regimen as well as with cytokine release syndrome. Any of these conditions including GvHD can be associated with fever. The skin is the most commonly involved organ, followed by the gastrointestinal (GI) tract and liver. A constellation of symptoms involving these organ systems may be helpful in establishing the diagnosis of GvHD. Diarrhea, rash, fever, and pancytopenia are common toxicities in the 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.

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 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 patients following bone marrow transplant.

Bone marrow suppression is also a feature of transfusion-related GvHD. To minimize the possibility of transfusion-related GvHD, all blood products transfused within 4 weeks prior to leukapheresis, within 4 weeks prior to initiation of conditioning chemotherapy and following conditioning chemotherapy until at least 4 weeks following T-cell infusion or until bone marrow recovery (whichever is longer) must be irradiated. Patients receiving steroids or other immunosuppressive therapies should also receive irradiated blood products regardless of above time intervals.

4.6.2 Grading of GvHD

Grading of GvHD is based on the stage of dermal, gastrointestinal, 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.

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 below (Glucksberg 1974).

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				

4.6.3 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 bone marrow transplant should be consulted.
- Consider biopsy of the affected organ(s)

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

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

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

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 anti-diarrheal regimen, dietary restrictions, volume replacement and consider initiation of non-absorbable steroids. For refractory or progressive symptoms consider systemic steroids as outlined below.

III	For more severe or progressive symptoms consider systemic corticosteroids (e.g., methylprednisolone one (1) mg/kg per day*)
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 bone marrow transplant expertise.

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

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

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

4.7 Chemotherapy Symptom Management

Cyclophosphamide and fludarabine are used as pre-conditioning lymphodepleting chemotherapy in this study. Symptoms associated with the use of cyclophosphamide and fludarabine are included in the respective product labels. Refer to the most current product label for each drug.

4.7.1 Management of Neutropenia

The pre-conditioning chemotherapy is intended to cause lymphodepletion. However, neutropenia is also common. Prophylactic use of G-CSF should be administered to all subjects. G-CSF should be used for management of neutropenia according to ASCO guidelines. G-CSF should be given daily from day +2 (RIB/regimens A and B) or 24 hours post the final dose of cyclophosphamide (Regimen C) and continued until reaching an absolute neutrophil count (ANC) of at least 1×10^9/L or per institutional practice.

According to institutional standard practice, long-acting (pegylated) G-CSF may be given in preference to short acting daily G-CSF. Pegylated G-CSF will be given as one dose on day +2 (Regimens A and B) or 24 hours post the final dose of cyclophosphamide (Regimen C).

4.7.2 Management of Pancytopenia with Bone Marrow Failure

Recurrent pancytopenia/aplastic anemia has been reported after initial bone marrow recovery from chemotherapy followed by infusion of NY-ESO-1^{c259}T cells. Bone marrow recovery following lymphodepletion will be defined as:

- Absolute neutrophil count $\geq$ 1 x10^9/L for 2 consecutive measurements and
- Platelet count $\geq$ 20 x10^9/L without transfusion support

Aplastic anemia is a rare hematological disorder characterized by pancytopenia and a hypocellular marrow. Patients 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 < 0.5 x10^9/L, absolute reticulocyte count < 60 x10^9/L, and platelet count < 20 x10^9/L, and myelodysplastic syndrome is ruled out. The clinical consequences of aplastic anemia are life-threatening bleeding from thrombocytopenia, and infection as a result of neutropenia. Bacterial and fungal infections are common and a significant cause of morbidity and mortality.

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

1. Consult a physician with expertise in the management of aplastic anemia
2. Increase the frequency of CBCs as clinically indicated.
3. Exclude other alternative etiologies such as other drugs, viral causes, etc.
4. An early bone marrow biopsy is recommended for clinical diagnosis, with a sample to be provided to the sponsor for study
5. A matched peripheral blood sample should be collected in parallel with the bone marrow sample and provided to the sponsor
6. Initiate treatment with GCSF
7. Consult an Infectious Diseases expert
8. Once alternative etiologies have been excluded, strongly consider immunosuppression (e.g. methylprednisolone 2mg/kg initial dose) or more aggressive regimens (e.g. antithymocyte globulin (ATG), cyclosporine, eltrombopag) as well as antimicrobial prophylaxis/therapy with the advice of your hematology/ID consultant(s). If high dose corticosteroids are initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

Please refer to Section 4.5 (Management of Graft-versus-Host Disease) regarding bone marrow suppression as a feature of GvHD.

5 Response Criteria

Objective response and progression will be primarily evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Committee (Eisenhauer 2009). Although criteria for progression may be reached at the Day 28 evaluation, determination of progression will not be made prior to confirmation by evaluation at Week 8, due to the potential for initial swelling and delayed tumor response in cell therapy regimens.

All imaging scans (CT or MRI) will also be collected and stored at a central imaging laboratory for independent review. Imaging scans of all areas affected by disease including, at minimum, the chest, abdomen and pelvis should be performed at Baseline and all subsequent visits. Acceptable imaging modalities for this study include:

- Diagnostic-quality CT scan with oral and/or i.v. iodinated contrast of the chest and abdomen/pelvis (CT is the preferred modality for tumor assessments)
- MRI of the abdomen/pelvis acquired before and after gadolinium contrast agent administration and a non-contrast enhanced CT of the chest, if a subject is contraindicated for contrast enhanced CT.

The same imaging modality and image-acquisition protocol (including the use of IV contrast) should be used consistently across all timepoints for individual subjects to allow uniform comparison of lesions. Prior to starting the study, a detailed imaging acquisition protocol will be provided to the sites.

5.1 Response Criteria for Radiographic Studies

In accordance with RECIST v1.1, at the baseline tumor assessment, a maximum of five (up to two per organ) reproducibly measurable lesions (≥10mm in longest diameter or, for lymph nodes, ≥15mm in the shortest diameter) will be determined as Target lesions and other tumor lesions or disease manifestations (e.g. ascites, effusions) recorded as Non-Target lesions. At each subsequent tumor assessment, changes in the sum of the diameters (unidimensional measurement) of all designated Target tumor lesions is used to assess outcome according to RECIST v1.1 criteria. In addition, perpendicular bi-dimensional measurements of Target lesions should also be made (where possible) and the sum of the products of the 2 largest perpendicular diameters are to be used to evaluate tumor burden in accordance with the principles of the immune related response criteria (irRC, Wolchok 2009).

5.2 Tumor Response Evaluation – RECIST v1.1

a. Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: determination of PD will require confirmation by an additional scan 4 weeks later unless the patient requires anti-cancer therapy sooner.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

b. Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD (Stable Disease, SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Unequivocal progression of existing non-target lesions may be considered PD for non-target lesions.

Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of New lesions

New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumor. Unequivocal new lesions constitute Progressive Disease, however, determination of PD will require confirmation by an additional scan 4 weeks later unless the patient requires anti-cancer therapy sooner.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or subject discontinuation from the study assessments (if the subject discontinued without evidence of radiologic progression). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The investigator's assessment of Best

Overall Response is performed according to the table below. Additional details of the evaluation of response according to RECIST v1.1 will be provided in the RAP.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD Not evaluated	No	PR	
SD	Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	≥4 wks. Confirmation
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

c. Patients with a global deterioration of health status requiring additional anti-cancer therapy without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

d. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesions be investigated (fine needle aspirate/biopsy, PET scan) before confirming the complete response status.

5.3 Confirmatory Measurement/Duration of Response

a. Confirmation

To be assigned a status of a CR, PR or PD, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met.

b. Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that progressive

disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

5.4 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded), as ≥10 mm (or twice the slice thickness, if a slice thickness >5 mm is used) with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

5.5 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

5.6 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

5.7 Target Lesions

Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target** lesions and measured and recorded at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameters), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Progressive disease by RECIST v1.1 criteria (Eisenhauer 2009) noted after the first re-staging scan may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required at the next scheduled re-staging evaluation unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected.

5.8 Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

5.9 Metastatic Bone Lesions

Disease progression is considered if a minimum of two new lesions is observed on bone scan. New lesions seen with the first re-staging bone scan may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required at the next scheduled re-staging bone scan unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected.

5.10 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

5.11 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

5.12 Methods of Measurement

Chest X-ray - Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI - CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Recommended slice thickness is 5 mm for chest, abdomen and pelvis lesions and 2-3 mm thickness for head and neck lesions. PET (alone) is currently not an acceptable method of assessment but may be used to confirm progression.

5.13 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

6 Statistical Considerations

6.1 Overview Statistical Methods

The primary objectives of this pilot trial are to evaluate (1) efficacy and (2) the safety of treatment with adoptively transferred NY-ESO-1^{c259}T cells. The data will be summarized by cohort and overall. No specific statistical hypotheses will be evaluated. All analyses will be descriptive and exploratory.

6.2 Study Populations and Subgroups

Intent-to-Treat (ITT) population: all subjects who were enrolled in the trial.

Modified Intent-to-Treat (mITT) population: all subjects who received at least one NY-ESO-1^{c259}T cell infusion. The mITT population is the primary analysis population for efficacy and safety evaluations.

If several subjects within a cohort are deemed major protocol violators, for example receiving a dose outside the range defined in Section 3.2.7, a per-protocol population may be evaluated. Decisions regarding subject eligibility for inclusion in the per-protocol population will be made prior to data analysis and reporting.

The following subgroups may be evaluated: (1) Subjects who receive a dose of at least 1 billion cells, (2) Subjects in Cohort 2 who receive Regimen A or C, (3) Subjects receiving a second infusion. Other subgroups may be defined in the RAP.

For cohorts where N≤5, for example Cohort 2 subjects receiving regimen C, the data may be listed only.

6.3 Statistical Assumptions

The sample size for each cohort is based on clinical judgment. The study is not statistically powered to conduct hypothesis testing between cohorts.

6.3.1 Cohorts 1, 3 and 4

Data from protocol 08-C-0121 0121 at the NCI, *Phase II Study of Metastatic Cancer that Expresses NY-ESO-1 Using Lymphodepleting Conditioning Followed by Infusion of Anti-NY ESO-1 TCR-Gene Engineered Lymphocytes* demonstrated that NY-ESO-1 specific T cells mediated objective responses (CR or PR by RECIST) in 4 of 6 (67%) patients with synovial sarcoma. The following table shows the probability of observing 5+ or 6+ responses in 10 patients as a function of the true underlying probability of a response:

True Response Probability	Number of patients achieving clinical response, assuming N=10	Probability of responding (as noted)
30% response rate	5 or more	0.15 probability
30% response rate	6 or more	0.05 probability
40% response rate	5 or more	0.37 probability
40% response rate	6 or more	0.17 probability
57% response rate	5 or more	0.78 probability

True Response Probability	Number of patients achieving clinical response, assuming N=10	Probability of responding (as noted)
67% response rate	5 or more	0.93 probability
67% response rate	6 or more	0.79 probability

Thus, if the true probability of a response were 0.67, there is a 79% probability of observing 6 or more responses and 93% probability of observing 5 or more responses. If the true probability were 0.30, these probabilities are 5% and 15% respectively. This would indicate that observing 5 or more responses out of 10 provides reasonable evidence that the true response rate could be consistent with 67%.

A lower response rate for example of 57% would also be clinically meaningful. The probability of observing 5 or more responders out of 10 subjects would be 78% given a true response rate of 0.57.

Should the trial dynamics result in >10 subjects in a cohort, holding all other variables constant, this would result in greater confidence. The table below illustrates this for the probability of observing 10+ or 12+ responses in 20 subjects as a function of the true underlying probability of a response. For example, the probability of observing 10 or more responders out of 20 subjects would be 0.80 given a true response rate of 0.57.

Therefore, even if the true response rate is lower than 0.57, clinically meaningful conclusions may be drawn from 10 subjects if five or more responses are observed and there is even more confidence with 20 subjects, holding all other variables constant.

True Response Probability	Number of patients achieving RECIST response, assuming N=20 in a cohort	Probability of responding
57% response rate	10 or more	0.80 probability
67% response rate	10 or more	0.96 probability
67% response rate	12 or more	0.82 probability

6.3.2 Cohort 2

A true response rate of 0.40 would be clinically meaningful in this cohort. The following table shows the probability of observing 3+ or 4+ responses in 10 patients as a function of the true underlying probability of a response equaling 40%:

True Response Probability	Number of patients achieving clinical response, assuming N=10	Probability of responding
40% response rate	3 or more	0.83 probability
40% response rate	4 or more	0.62 probability

Thus, if the true probability of a response were 0.40, there is a 62% probability of observing 4 or more responses and 83% probability of observing 3 or more responses. This would indicate that observing 3 or more responses out of 10 provides reasonable evidence that the true response rate could be consistent with 40%.

6.3.3 Stopping Criteria for Cohorts 2, 3 and 4

As discussed in Section 3.2, the decision to stop or continue enrolment to Cohorts 2, 3 and 4 after first 5 subjects is based on responses seen with these 5 subjects. Futility evaluations using predictive probability in a Bayesian framework coupled with clinical judgment will aid in this decision making. The advantages of a Bayesian framework in an early phase study with smaller sample size is that it allows one to make decisions without relying on large sample theory in addition to being able to incorporate prior information. The cohorts under study are not powered to test hypotheses and therefore, type II error has not been controlled.

The predictive probability is the probability of exceeding a response rate of interest at the end of the trial with the maximum planned sample size N_{max} (up to 10), given the results from the initial group (i.e., n=5). Assuming a historical control rate of 0.18, one-sided futility assessments are planned for cohorts 2 to 4 based on response rates of interest ranging from 0.18, 0.25, 0.5.

Therefore 0.18 represents the response rate for the historical control whereas, 0.5 is the projected clinically meaningful response rate for TCR as seen in cohort 1 with 12 subjects. The 95% (Wilson) confidence interval for the response rate of 6/12 = 0.5, seen in cohort 1 is (0.25, 0.75). This implies that repeated clinical trials would result in ORR estimates ranging from 0.25 up to 0.75. As such the lower bound of 0.25 is considered clinically relevant to evaluate for futility.

To compute the predictive probability (PP), we assume a fairly non-informative prior distribution, i.e., a beta (0.18, 0.82) for the ORR. This prior was chosen as it may be viewed as somewhat pessimistic and supportive of the historical control rate. Under the assumption that the number of responses X in n=5 subjects follows a binary distribution B(n, p), the posterior distribution of the ORR follows a beta(0.18+x, 0.82+n-x) distribution. This then means that the future number of responses, Y in m = N_{max} - n follows a beta-binomial (m, 0.18+x, 0.82+n-x) distribution. Using methods described in Lee and Liu (2008), the predictive probability is derived for N_{max} =10 as shown in the table below.

A threshold of 0.2 is used to declare futility, i.e. if PP < 0.2 then the cohort has met the futility criterion.

Table 3: Predictive Probability that ORR Exceeds Pre-identified Rate at Nmax =10, Having Observed X responses in 5 Subjects

ORR of interest	X=0/5	X=1/5 *	X=2/5	X=3/5	Futility (PP < 0.2)
0.18	0.0016	0.109	0.548	0.932	Yes X=0,1
0.25	0.0002	0.033	0.302	0.773	Yes X=0,1
0.50	0	0	0.031	0.299	Yes X=0,1,2

* if 1/ 5 responses are observed the PP that ORR > 0.25 is 0.033, which is < 0.2 (the futility threshold), so the futility criterion has been met.

- When X = 0 or 1 the PP meets the futility threshold for all the scenarios of ORR of interest considered above.
- Likewise when X > 2, the PP does not meet the futility criterion and hence the cohort will continue to N_{max} subjects.

When X = 2/5 (i.e., p=0.4), the PP ranges from 0.031 to 0.548 depending on whether the rate is 0.50, 0.25 or 0.18 and hence futility is declared for the probability that ORR exceeds 0.50 but not

for the other two scenarios. Note that in this case the ORR of 0.4 leads to a 95 % (Wilson) CI of (0.12, 0.77). The small sample size leads to a high degree of imprecision and therefore a high chance of a type II error (even if this trial is not powered to test the hypothesis). Thus, clinical judgment will also be employed in the decision to stop a cohort as indicated earlier.

6.4 Statistical Methods for Efficacy Endpoints

To determine the effect of the treatment, the following efficacy parameters will be summarized: overall response rate (ORR); time to response (TTR), duration of response (DoR), best overall response (BOR); progression free survival rate (PFS); and the overall survival rate (OS).

Primary Analyses – The primary efficacy endpoint is ORR. ORR is defined as the proportion of subjects with a confirmed CR or PR per RECIST v1.1 relative to the total number of subjects in the corresponding analysis population. The ORR will be based on confirmed responses from the investigator assessment of overall response. Subjects with unknown or missing response will be treated as non-responders (i.e., they will be included in the denominator when calculating the proportion). 90% and 95% Wilson confidence intervals will be computed for ORR in each cohort.

Secondary Analyses – The key secondary endpoints are DoR, PFS and OS.

Duration of overall response is defined as the time between confirmed response until the first date of progressive disease per RECIST v1.1 (see Section 5.2). DoR will be summarized descriptively for subjects for each cohort using Kaplan-Meier quartile estimates.

Overall Survival is defined as the interval between date of T-cell infusion and death due to any cause. If the subject does not have a documented date of death, OS will be censored at the date of the last adequate assessment.

PFS is defined as the interval between the date of first dose and the earliest date of disease progression or death due to any cause. PFS will be summarized by cohort sing Kaplan-Meier quartile estimates. If the subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment.

OS and PFS will be summarized graphically for each cohort using Kaplan-Meier plots.

Further details about the primary and other secondary efficacy/exploratory analyses will be outlined in the RAP, for example, sensitivity analyses, details for rules for censoring, etc.

6.5 Statistical Methods for Safety and Demographic Endpoints

The safety profile will be based on adverse events reported, vital signs measurements, clinical laboratory measurements, ECG recordings, and physical examination results.

Adverse Events – All adverse events will be listed and coded by MedDRA. The number and percent of patients reporting any treatment emergent adverse events will be tabulated by system organ class and preferred term. Adverse events with missing date of onset will be considered treatment emergent. Adverse events will be further summarized by severity, relationship to treatment and seriousness. Tables and/or narratives of any on study death, or serious or significant adverse event, including early withdrawals from the interventional period because of adverse events, will be provided should they occur.

Vital Signs – Vital signs will be listed for each patient. Summaries of vital signs data over time may be provided.

Electrocardiogram – Electrocardiogram data will be listed for each patient. Fridericia'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.

Anti-NY-ESO-1 Antibodies – The patient incidence of Anti- NY-ESO-1 antibody formation will be computed and the anti- NY-ESO-1 Antibodies results will be listed.

T cell Phenotype and Cytokines – Exploratory correlations with clinical outcomes may be performed.

Clinical Laboratory Tests – Clinical chemistry, hematology, and urinalysis data will be listed for each patient. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Summaries of clinical laboratory tests over time may be provided. Laboratory abnormalities will be graded using CTCAE version 4. Each patient'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.

Descriptive statistics will be provided for selected demographic assessments such as age, gender, prior chemotherapy, etc.

For descriptive statistics, continuous data will be summarized using means, medians, standard deviations, and/or ranges. Categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

7 Human Subjects Protections

7.1 Participation of Children

The age range of patients eligible for this trial is ages ≥4 and up. All patients <18 years of age (or relative country-specific guidelines) will be enrolled at participating sites. Physicians, nurses, and multidisciplinary support teams for these subjects must have expertise in the management of children.

7.2 Evaluation of Benefits and Risks/Discomforts

7.2.1 Potential Benefit of Adoptive Immunotherapy

Survival for the population of patients eligible for this trial is limited. Although the overall treatment plan is experimental, preliminary data from a study conducted in adults demonstrated significant antitumor effects, therefore, there is reason to believe that patients enrolled on this study will derive benefit. Patients participating in this trial will be treated with therapeutic intent, and the response to therapy will be monitored. The potential benefits from adoptive immunotherapy for synovial sarcoma are disease remission and/or reduction in cancer-related symptoms. This protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects according to 21CFR50.52, 46.405.

7.2.2 Potential Risks of Adoptive Immunotherapy

The primary risks to patients participating in this research study include toxicity of the chemotherapy, as described in Section 7.2.3, and the potential risks associated with infusion of autologous modified T cells engineered to express antigen receptors to a known tumor antigen.

Toxicities relating to the infused gene modified T cells potentially include infusion reactions, cytokine release syndrome, and effects of the cells themselves including autoimmunity and graft-versus-host disease. The full safety profile for NY-ESO-1^{c259}T has not yet been established. See Section 4 for recommendations on supportive care of patients on this study including strategies for management of the above possible toxicities.

7.2.3 Potential Risks of Lymphodepleting Chemotherapy

Lymphodepleting drugs used in this protocol are standard chemotherapy agents with the expected toxicities of myelosuppression. Grade 3 or 4 hematological toxicity may occur and are expected. There is an increased risk of infection during the neutropenic period, so patients will be supported using G-CSF as well as transfusions. The agents are also immunosuppressive (hence their use as lymphodepleting therapy). Patients may receive prophylaxis against PCP pneumonia, invasive fungal infection, herpes simplex and herpes zoster according to institutional practice.

7.2.4 Potential Risk of Tumor biopsy

In the event a patient has a readily accessible tumor, adult patients will be asked to undergo biopsy in order to obtain tissue for research evaluation. Standard techniques will be used for percutaneous biopsies and may include CT and / or ultrasound guidance. Although direct benefit from research conducted on this tumor biopsy is unlikely, participation in this research may allow patients some benefit in knowing their contribution may lead to a greater understanding of their cancer and potential benefit to others in the future. Patients enrolled on this protocol suffer from extremely rare malignancies with very low survival rates and often have a strong desire to participate in research that may lead to a better understanding of their disease.

7.2.5 Potential Risk of Acute inflammatory demyelinating polyneuropathy / Guillain Barré Syndrome (GBS)

Acute demyelinating peripheral neuropathy / Guillain Barré Syndrome (GBS) developed in two subjects who received the NY-ESO-1^{C259}T cells following infusion. Therefore, subjects with prior or active demyelinating disease will be excluded from the study. Neurologic consultation is required for patients with Grade 2 or higher neurologic events of a ≥7 day duration. Additionally, any potential future recurrence of GBS will lead to a pause in study enrolment until further investigation.

7.3 Consent and Assent Processes and Documentation

7.3.1 Screening Sample Consent

Telephone consent may be employed in order to screen outside samples for prospective subjects for NY-ESO-1, if not previously conducted by the outside institution. In such cases, a protocol investigator will review the Screening Consent form by telephone. The consent/assent signatures will be witnessed and a copy will be faxed and the original sent by mail to the PI. Prospective subjects who consent to send such samples for outside testing will NOT be registered with the Sponsor unless they are subsequently enrolled on protocol. Subjects and their referring medical team will be notified of the results and records will be maintained with the protocol research files.

7.3.2 Protocol Consent

A signed informed consent document will be obtained prior to entry onto the study. The PI or an associate investigator on the trial will obtain consent. The PI, an Associate Investigator, or their designee will be available to answer all questions from patients and their parents or guardians. The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and potential benefits, and alternative therapies will be carefully explained to the patient and/or the patient's parents or guardian if he/she is of minor age. Pediatric patients will be included in age appropriate discussion. Verbal assent will be obtained for those > 7 years of age when deemed appropriate by the clinician and the child's parents or guardian. In such cases, the parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent. The attached informed consent documents contain all elements required for consent.

8 Data Reporting

8.1 Safety Reporting

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. Individual AEs should be evaluated by the Investigator and should be reported to the Sponsor as appropriate. This includes the evaluation of its intensity, the causality between the investigational medicinal product and/or concomitant therapy and the adverse event 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. The Sponsor has obligations for expedited reporting of certain events to Regulatory Authorities, IRBs/ Research Committees and other study participants. On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor will submit detailed records of all adverse events which are reported to him by the relevant Investigator(s). Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases

8.2 Definition of Adverse Event

In accordance with the International Conference of Harmonization (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 a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Disease progression will not be reported as an AE, however other pre-existing conditions which worsen during the study are to be reported as AEs.

Additionally for this study, all laboratory abnormalities with a CTCAE grading of grade 3 or above must be reported as an adverse event.

8.3 Reporting of Adverse Events

Subjects will be monitored for the duration of the protocol, including intervals required as part of long-term follow-up. The AE reporting period begins at the start of lymphodepletion and continues until the subject has confirmed disease progression following the subject's last cell product infusion. During the period between leukapheresis and lymphodepletion, only serious adverse events (SAEs) related to the study procedure which occur within 2 weeks of leukapheresis will be reported. During long term follow-up (15 years), subjects will only be monitored for delayed adverse events related to the gene transfer aspect of the protocol (see Section 3.11.2 for LTFU).

Adverse events will be graded according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v 4.0.

All reported adverse events, signs or symptoms or abnormal laboratory findings should be recorded at every visit according to the appropriate diagnosis and rated for intensity, causality and seriousness. In the absence of a diagnosis, individual symptoms or findings should be recorded and rated. 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 discontinuation of the subject from the interventional portion of the study, or withdrawal from the study, serious or severe adverse events will be followed until one of the above criteria is met for up to 4 weeks. Serious adverse events related to investigational product will continue to be recorded and monitored into long-term follow-up at any time (Section 10.4).

8.3.1 Assessment of Intensity

The investigator will assess intensity of all AEs will be graded according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v 4.0 on a five point scale (grade 1-5) and reported in detail on the eCRF.

AEs not specifically listed on the CTCAE should be graded according to Table 4:

Table 4: Grading of AEs not specified in CTCAE v4.0

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.

8.3.2 Assessment of Causality

The investigator will assess the causal relationship between the adverse event and investigational product according to his/her best clinical judgement.

8.4 Reporting Serious Adverse Events (SAEs)

An SAE is any adverse event that:

- Is fatal (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 in-subject hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant disability or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is clinically significant or requires intervention or prevent one or the outcomes listed above.

Medical and scientific judgment should be exercised in deciding if an adverse event is of significant enough medical importance to be classified as serious outside the above definitions. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject 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 cytokine release syndrome or GvHD, and all cases of Guillain Barré syndrome or other demyelinating neuropathies 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 recorded by completing the SAE eCRF form within the electronic data capture (EDC) system. In addition, an SAE Worksheet must be completed and submitted to GSK within 24 hours by e-mail to PPD and PPD (or fax: PPD PPD).

Details pertaining to the SAE must be completed by the Investigator with as much available information about the event. The minimum reporting criteria for an SAE include:

- Identifiable subject (Subject ID)
- Event that is identified as serious (SAE term)
- Severity and grading
- Suspect medicinal product
- Relationship to suspect medication
- 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 investigational product according to his/her best clinical judgement. Further details can be found in the Study Procedures Manual.

8.5 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 guidance (Guidance for Industry, Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events; November 2006). Subjects will be followed according to the schedule outlined in Section 3.11.2. Emergence of any of the following new clinical conditions reported or observed and the action taken will be reported to the Sponsor:

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

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.

8.6 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 cardiovascular (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

8.7 Management of Encephalopathy Syndrome

Encephalopathy has been described in association with chimeric antigen receptor (CAR) T therapy, and termed (CAR) T cell related encephalopathy syndrome, or CRES (Neelapu et al, 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 6), 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.

Encephalopathy syndrome (ES) may occur with other cancer immunotherapies, including TCRs. Cancer patients may also be at risk for encephalopathic 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 encephalopathy syndrome in relation to T cell therapy.

8.7.1 Grading of ES

Neelapu et al (2018) have developed a new grading system for ES which incorporates the CARTOX 10 point neurological assessment (CARTOX 10) tool, see Table 5. Points are assigned for each of the tasks in Table 1 which are performed correctly. Normal cognitive function is defined by an overall score of 10.

The CARTOX-10 should be used to monitor all subjects for ES.

Table 5: CARTOX 10−point neurological assessment (CARTOX-10)

Task	CARTOX Points
Orientation to: year, month, city, hospital, and President/Prime Minister of country of residence	Total of 5 points (one point for each)
Name three objects, for example point to: clock, pen, button	Total of 3 points (one point for each)
Write a standard sentence, eg. '*our national bird is the bald eagle*'	1 point
Count backwards from 100 in tens	1 point

The CARTOX-10 score is used in grading of ES as presented in Table 6.

Table 6: Grading of Encephalopathy Syndrome (ES), based on Neelapu et al. 2018

Symptom or sign	Grade 1	Grade 2	Grade 3	Grade 4
Neurological assessment score (by CARTOX−10[1])	7–9 (mild impairment) if different from baseline	3–6 (moderate Impairment)	0–2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks
Raised intracranial pressure	NA	NA	Stage 1–2 papilloedema[2], or CSF opening pressure <20 mmHg	Stage 3–5 papilloedema[2], or CSF opening pressure ≥20 mmHg, or cerebral oedema
Seizures or motor weakness	NA	NA	Partial seizure, or non−convulsive seizures on EEG with response to benzodiazepine	Generalized seizures, or convulsive or non-convulsive status epilepticus, or new motor weakness

[1] See Table 1 for CARTOX−10.

[2] Papilloedema grading is performed according to the modified Frisén scale.

8.7.2 Monitoring for ES

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.

CARTOX-10 should be measured on the day of NY-ESO-1c259T 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 MAGE-A4c1032T infusion. If a subject is found to have ES, the CARTOX-10 should be used at least twice per day until resolution or stable. It can also be used at later visits if indicated.

8.7.3 Management of ES

The recommended management of ES should be based on toxicity grade. Table 7 provides guidance on the management of ES, and should be implemented in accordance with institutional guidelines.

Grade 1 ES 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 ES in the setting of CRS. In the setting of concurrent CRS, for Grades 1-3 ES 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 ES for thorough neurological evaluation, and recommendations for further testing such as EEG and neuroimaging as indicated.

Table 7 Management of encephalopathy syndrome (CRES)

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 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 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] IV or siltuximab 11 mg/kg IV, if Grade 1 persists beyond 24 hours, or worsening and associated with concurrent cytokine-release syndrome (CRS)
2	• Supportive care and neurological work−up as described for grade 1 ES • 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 ES without concurrent CRS; Once initiated continue corticosteroids until improvement to grade 1 ES and then taper • Consider transferring patient to intensive-care unit (ICU) if ES associated with grade ≥2 CRS
3	• Supportive care and neurological work−up as indicated for grade 1 ES • ICU transfer is recommended • Anti−IL−6 therapy if associated with concurrent CRS if not administered previously • Corticosteroids as outlined for grade 2 ES if symptoms worsen despite anti−IL−6 therapy, or for ES without concurrent CRS; continue corticosteroids until improvement to grade 1 ES 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 ES
4	• Supportive care and neurological work−up as indicated for grade 1 ES • 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 ES • High-dose corticosteroids continued until improvement to grade 1 ES 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.

8.8 Pregnancy

There is no preclinical or clinical trial data of NY-ESO-1c259T 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 2.3.1 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.

8.9 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	24 hours	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the CV 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 CV 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 Follow up- Form

9 Data Safety Monitoring Plan

The Sponsor is responsible for review of all adverse events and the Principal Investigators will be responsible for reporting all adverse events. The Sponsor, Principal Investigators, and research teams can meet or teleconference at frequent or regularly scheduled intervals, to determine treatment modifications and treatment based toxicities, to monitor trends in adverse events, and determine if trends are noted, as needed.

The Sponsor is responsible for monitoring toxicity trends on this study. The Sponsor will report to the site IRB/IEC on at least an annual basis according to the institutions policy on continuing reviews.

This study will be monitored by the Sponsor or their designee.

9.1 Safety Review Team

A SRT will be implemented in this study. In line with routine pharmacovigilance, a GSK SRT will review blinded 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. A SRT charter, defining roles and accountabilities and the process for safety review and meeting frequency, will be available.

9.1.1 Mandated Study Pause Due to GBS

The occurrence of any event of GBS will mandate a pause in enrollment and stopping treatment for all participants within the GSK3377794 studies.

9.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, the Sponsor will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- Sponsor will provide full details of the above procedures, either verbally, in writing, or both.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission. Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10 Appendices

10.1 Appendix 1: Performance Status

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10.					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	**Description**	**Score**	**Description**	**Score**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction.	100%	Normal, no complaints, no evidence of disease.	100%	Fully active, normal.
		90%	Able to carry on normal activity; minor signs or symptoms of disease.	90%	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory, able to carry out light or sedentary work, e.g., light housework, office work.	80%	Able to carry on normal activity with effort; some signs or symptoms of disease.	80%	Active, but tires more quickly.
		70%	Cares for self, unable to carry on normal activity or do active work.	70%	Both greater restriction of, and less time spent in, play activities.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60%	Requires occasional assistance but is able to care for most of own needs.	60%	Up and around, but minimal active play; keeps busy with quieter activities.
		50%	Requires considerable assistance and frequent medical care.	50%	Gets dressed, but lies around much of the day; no active play; able to participate in quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40%	Disabled; requires special care and assistance.	40%	Mostly in bed; participates in quiet activities.
		30%	Severely disabled; hospitalization indicated, although death not imminent.	30%	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to a bed or chair	20%	Very ill; hospitalization necessary; active supportive treatment required.	20%	Often sleeping; play entirely limited to very passive activities.
		10%	Moribund, fatal process progressing rapidly	10%	No play; does not get out of bed
5	Dead	0%	Patient expired	0%	Unresponsive; Dead

10.2 Appendix 2: Schedule of Procedures

	Screening and Baseline			Interventional Phase																									
	Screening		Baseline	Days												Weeks								Months					Every 3 months until 2 years, every 6 months until 5 years, until progression/ discontinuation[n]
Labs, Tests, Procedures	Within 7 days of apheresis	Apheresis	Within 7 days prior to chemo	-7	-6	-5	-4	-3	-2	-1	0[b]	1[b]	3[b]	4[b]	7[b]	2	3	4	5	6	8	10	12	4	5	6	9	12	
Tests and Procedures																													
Informed Consent	X[a]																												
History	X		X																										
Physical Exam	X		X								X	X	X	X	X	X	X	X		X	X		X	X		X	X	X	X
Adverse Events/ConMeds [m]		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CARTOX-10 neurological assessment tool	X										X	X	X	X	X														
HLA-A2	X[c]																												
NY-ESO-1 Expression	X[c]																												
Drug Administration																													
Regimen A chemotherapy[d,e]						X	X	X	X																				
Regimen B chemotherapy[d,e]								X	X																				
Regimen C chemotherapy[d,e]				X	X	X																							
NY-ESO-1^{c259}T											X																		
Lab Tests & Procedures																													
Large Volume Apheresis		X																											
Disease Staging-CT / MRI	X		X															X			X		X			X	X	X	X
Urinalysis	X		X																										
Hematology	X		X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X		X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]		X	X	X	X	X	X	X	X		X	X		X	X		X	X	X	X
CMV PCR			X								X					X		X		X	X								
PT, PTT	X		X																										
Amylase/Lipase			X																										
Ferritin			X																										
GFR / creatinine clearance[p]			X																										

	Screening and Baseline			Interventional Phase																										
	Screening		Baseline	Days												Weeks								Months					Every 3 months until 2 years, every 6 months until 5 years, until progression/ discontinuation[n]
Labs, Tests, Procedures	Within 7 days of apheresis	Apheresis	Within 7 days prior to chemo	-7	-6	-5	-4	-3	-2	-1	0[b]	1[b]	3[b]	4[b]	7[b]	2	3	4	5	6	8	10	12	4	5	6	9	12	
Virology	X[f]																												
Thyroid Panel			X[g]																										
ANA			X[g]																										
Rheumatoid Factor			X[g]																										
Lab Tests & Procedures																													
Pregnancy[q]	X		X																										
Echo or MUGA	X																												
ECG	X		X																										
Brain MRI	X																												
Vector Copies (Persistence for Safety) [l]			X																				X			X		X	X
VSV-G DNA (RCL) for safety			X																				X			X		X	X
Research Studies:																													
Tumor biopsy			X[h]																		X[i]								X[j]
Serum Cytokines			X								X[k]	X		X	X	X	X	X		X	X								
Vector Copies (Persistence for Research)			X											X	X	X		X			X								
Flow Cytometry			X												X			X			X					X		X	X

Notes:

[a] Written subject informed consent must be obtained prior to performing any protocol procedures. The Tissue/Screening Informed Consent Form will be signed prior to tumor sample collection during screening, and the Treatment Informed Consent will be signed prior to all other remaining screening procedures

[b] Days 1 to 7 obtain physical examination, adverse events, concomitant medications, hematology, chemistry on at least 3 separate days

[c] Any time prior to apheresis

[d] Patients may be admitted to the hospital for administration of chemotherapy and remain hospitalized until recovery of ANC to >0.5x10^9/L. Chemotherapy conditioning may also be performed as an outpatient procedure at the discretion of the PI. Chemotherapy will be given with supporting therapy as described in Section 3.3

[e] G-CSF should be given daily from Day +2 (Regimens A and B) or from 24 hours post chemotherapy (Regimen C) until ANC >1.0x10^9/L, or per institutional guidelines as described in Section 4. Long-acting (pegyated) G-CSF may be substituted according to institutional practice as described in Section 4

[f] Within 1 month of apheresis
[g] Within 8 weeks of initiating chemotherapy, unless clinically indicated to be repeated prior to chemotherapy initiation
[h] The baseline biopsy material may be collected anytime between two months and two weeks (±1 week) prior to the start of chemotherapy, with a preference for the biopsy to be taken closer to the time of infusion
[i] The biopsy scheduled post therapy may be taken ±4 weeks of the week 8 visit
[j] The tumor biopsy at this time point is for disease progression/study discontinuation only, not every 3 months
[k] Pre-infusion and any time from 1 hour post-infusion or later at the discretion of the investigator or if clinically indicated. Levels should also be obtained if clinical symptoms of cytokine release syndrome develop
[l] Persistence will be taken at Baseline (any time prior to cell infusion), Month 3, 6, 12, then every 6 months until 5 years post-infusion and until no gene modified cells are detected (i.e. not required at every visit). If no gene modified cells are detected at 5 years, patients may be followed by postcard or phone call
[m] Refer to Section 8.3 for reporting of adverse events
[n] Subjects who remain in the interventional phase of the study at 5 years post treatment will then be assessed according to the Long Term Follow Up schedule in Appendix 4
[o] Hematology and serum chemistry are required only on the days the patient receives chemotherapy during conditioning
[p] Required for patients ≥65 yrs age
[q] Pregnancy test for WOCBP only. Urine or serum pregnancy test is to be performed and confirmed negative at screening and at baseline. Pregnancy test (urine or serum per local requirements) is required within 24 hours before first dose of study intervention.

10.3 Appendix 3: Off-Treatment Procedures

(One time only; at discontinuation)	
History & Physical, vital signs & weight	X
Laboratory	
• Hematology	X
• Chemistry*	X
• Flow cytometry	X
Disease Restaging	X

* LDH, ALT, AST, alk phos, bilirubin (total and direct), BUN/urea, creatinine, electrolytes, Ca, Mg, PO_4, uric acid, albumin.

10.4 Appendix 4: Long-Term Follow-Up Schedule

Time post-infusion	Year 1			Year 2		Year 3		Year 4		Year 5		Years Post-infusion[b]									
	3 mo	6 mo	1 yr	1yr 6 mo	2 yr	2 yr 6 mo	3 yr	3 yr 6 mo	4 yr	4 yr 6 mo	5 yr	6	7	8	9	10	11	12	13	14	15
Clinical Assessments																					
Medical History[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X	X	X	X	X	X	X	X	X	X										
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemotherapies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VSV-G DNA (RCL) for safety[d]	X	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
Vector Copies (Persistence) for safety[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Overall Survival		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Including any changes in medical history since last visit
[b] Subjects who do not have persistence of gene modified cells may be followed remotely during years 6-15. In this case, physical exam, vector copied, and RCL will not be collected.
[c] 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 immune-related hematologic disorder.
- Serious infections (including opportunistic).
- Unexpected illness and hospitalization deemed related to gene therapy.

[d] RCL samples collected annually after the first year post infusion
[e] Month 3, 6, 12, and annually until year 5 and until no gene modified cells are detected.
[f] Only concomitant medications for the treatment of AEs related to NY-ESO-1^{c259}T will be collected

10.5 Appendix 5: Draft letter to patients and physicians for long term follow-up for delayed adverse events

10.5.1 Draft Patient Letter

[date]

[name and address]

Dear [patient name],

You have participated in a clinical research study that requires the study doctors and nurses to monitor your health for 15 years. In addition to the semi-annual and annual visits you will be attending, **we would like for you to report certain events listed below to your study doctor or nurse if they occur**:

1. Your doctor tells you that you have been diagnosed with any new type of cancer, including blood disorders such as leukemia or lymphoma (this would be separate from your diagnosis of multiple myeloma).
2. You develop loss of feeling in any part of your body, especially hands and feet; you develop a loss of control of any body part (arms, legs…); you have a seizure; you experience memory loss. In addition, if you experience a worsening of any of the symptoms listed, please contact your study nurse or doctor. These types of symptoms are called neurological disorders. If your primary doctor or specialist tells you that you have developed neurological symptoms, contact your study doctor or nurse.
3. You develop arthritis or autoimmune disease, or worsening of any previously experienced arthritis or autoimmune disease which you were experiencing prior to participation in the study. If you are experiencing symptoms of arthritis or have been told by your doctor that you have an autoimmune disease, contact your study doctor or nurse.

If you experience any of these events, please contact your study physician or the study nurse listed below as soon as you can. They may ask you questions about your health and will record your symptoms/disease and then monitor your health if they decide that it is necessary. When you call, please mention the protocol number of your study which is #(XXXXXX), or the brief study title which is "A pilot study of genetically engineered NY-ESO-1 specific (c259) T cells in HLA-A2+ patients with synovial sarcoma". Your patient identification number under this protocol is (#XXX).

Study Coordinator:
Name
Address
Phone
Email

If you have any questions about this letter or the follow up procedures for the study itself, please do not hesitate to contact the above study nurse or doctor.

Thank you for your continued participation in our clinical research study. Best regards,

[study coordinator]

10.5.2 Draft Physician Letter

[date]

[name and address]

Dear [physician name],

Your patient [patient name] has participated in a clinical research study that requires 15 year monitoring for adverse events. To aid in reporting of adverse events that are possible related to the clinical research study, we are asking the patients on our research study to designate a primary care or infectious disease physician that may help in the monitoring and reporting of adverse events. Your patient has designated you. **If upon any of your visits with your patient, any of the following events are reported or discovered, please contact the study nurse or physician as soon as possible**:

New malignancies

New incidence of exacerbation of a pre-existing neurologic disorder

New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder

New incidence of a hematologic disorder.

Unexpected illness and hospitalization deemed related to gene therapy

If your patient experiences any of these events, please contact the study coordinator below as soon as you can so that they can record the event and then monitor your patient's health if necessary. When you call, remember to mention the protocol number of the study which is #( ), patient ID (#) and the study title which is "A pilot study of genetically engineered NY-ESO-1 specific (c259) T cells in HLA-A2+ patients with synovial sarcoma".

Study Coordinator

Name

Address

Phone

Email

If you have any questions about this letter or the study itself, please do not hesitate to contact the above study nurse or physician.

Thank you for your support in helping us to monitor for delayed adverse events. Best regards,

[study coordinator]

10.6 Appendix 6: Liver Safety Required Actions and Follow up Assessments

Level 1 Monitoring

In the event that the subject develops elevations in LFT parameters as defined below, an increase to liver chemistry monitoring i.e. at weekly intervals, will apply.

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

Level 2 Monitoring

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

Liver Chemistry Monitoring Criteria Level 2	
ALT-absolute	ALT ≥5x ULN
ALT Increase	ALT ≥3x ULN that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3x ULN **and** bilirubin ≥ 2x ULN (>35% direct bilirubin)
INR[2]	ALT ≥3x ULN **and** INR>1.5

<table>
<tr><td>Symptomatic[3]</td><td>ALT ≥3x ULN and associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.</td></tr>
<tr><td colspan="2">Required Actions and Follow up Assessments</td></tr>
<tr><td>Actions</td><td>Follow Up Assessments</td></tr>
<tr><td>• 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 participant until liver chemistries resolve, stabilize, or return to within baseline (pre-Gene Therapy) (see MONITORING below)

MONITORING:
<u>For bilirubin or INR criteria:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline (pre-Gene Therapy)
• A specialist or hepatology consultation is recommended
For All other criteria:</td><td>• Viral hepatitis serology4
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2x ULN
• If possible, obtain peripheral blood for persistence of genetically modified cells.
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

<u>For bilirubin or INR criteria:</u>
• 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.</td></tr>
</table>

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin, INR) and perform liver event follow up assessments within **24-72 hrs** Monitor participants at least weekly until liver chemistries resolve, stabilize or return to within baseline (pre-Gene Therapy)	

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

10.7 Appendix 7: Summary of Changes from Amendment 14 to Amendment 15

Primary reason for this 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 GSK3377794 during clinical trials..

Section of Amendment 15	Change
2.2	Addition of Prior or active demyelinating disease as an exclusion criterion.
4.5	Addition of Monitoring and Management for Demyelinating Neuropathy and other Neurological events
7.2.5	Update to risk assessment to add additional risk of Guillain-Barré syndrome and other demyelinating neuropathies.
8.4	Addition of all cases of Guillain-Barré syndrome or acute demyelinating neuropathy as a reportable SAE within 24 hours.
9.1	Addition of GSK SRT
9.1.1	Addition of Mandated Study Pause due to GBS

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