TITLE: A Phase I/IIa, Open Label, Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer

Final Version: 07 February 2017

CONFIDENTIALITY STATEMENT

DECLARATION

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

A Phase I/IIa, Open Label Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific For NY-ESO-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer

Study Sponsor:	Adaptimmune Ltd 57c Milton Park Abingdon Oxon OX14 4RX www.adaptimmune.com
Study Drug:	**NY-ESO-1^{c259}T**
Protocol Number:	**ADP-0011-001**
IND Number:	**14603 (NY-ESO-1^{c259}T)**

Summary of Changes

Refer to Appendix H for a summary of the changes included in this amendment.

Date:	July 15, 2011	NIH RAC
Amended:	September 29, 2011	Initial Institutional Board reviews
Amended:	November 14, 2011	Institutional Board reviews
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Amended:	July 21, 2014	Version 4
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SIGNATURES AND AGREEMENT WITH THE PROTOCOL

I, the undersigned, have reviewed the protocol, including the appendices, and I will conduct the clinical study as described and will adhere to International Conference on Harmonisation (ICH) guideline E6 (r1):Guideline for Clinical Practice (GCP) and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigators Brochure.

Investigator Name	
Investigator Title	
Investigator Site and Address	
Investigator Signature	
Date	

RESPONSIBLE SPONSOR STUDY PHYSICIAN/SPONSOR INFORMATION PAGE

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AE, Adverse event
ASC, American Society of Clinical Oncology
ATC, Autologous T Cell
BOR, Best overall response
CFR, code of federal regulations
CMV, Cytomegalovirus
CR, Complete Response
CRF, case report form
CRM, Continual Reassessment Method
CRS, Cytokine Release Syndrome
CT, Cancer testis
CTC, common toxicity criteria
CTCAE, Common Terminology Criteria for Adverse Events
CTX, chemotherapy
CTL, cytotoxic T lymphocyte
DFS, Disease free survival
DSMB, data safety and monitoring board
DTC, dose-toxicity curve
ECHO, Echocardiogram
EFS, Event Free Survival
EKG, Electrocardiogram (or ECG)
FDA, food and drug administration
GCP, good clinical practices
G-CSF, Granulocyte colony-stimulating factor
GMP, good manufacturing practices
HAIC, Humoral anti-infused cell response
IB, Investigators Brochure
IBC, Institutional Biosafety Committee
IRB, Institutional Review Board
irRC, Immune-related Response Criteria
IV, intravenously
LTFU, Long term follow-up
MUGA, Multigated acquisition scan

NCCN, National Comprehensive Cancer Network

NCI, National Cancer Institute

ORR, Overall response rate

OS, Overall survival

PBMC, peripheral blood mononuclear cells

PD, Progressive disease

PFS, Progression free survival

PR, Partial response

RAC, NIH Office of Biotechnology Recombinant DNA Advisory Committee

RECIST, Response Evaluation Criteria in Solid Tumors

RCL, Replication competent lentivirus

RPCI, Roswell Park Cancer Institute

SD, Stable disease

TCR, T cell receptor

TIL, Tumor infiltrating lymphocyte

Treg, T regulatory cell; a T cell characterized by CD25/FOXP3 staining which suppresses effector T cell function.

STUDY SUMMARY

Title	A Phase I/IIa, open label clinical trial evaluating the safety and efficacy of autologous T cells expressing enhanced TCRs specific for NY-ESO-1 in patients with recurrent or treatment refractory ovarian cancer.
Short Title	CT Antigen TCR-redirected T cells for ovarian cancer.
Protocol Number	**ADP-0011-001**
Phase	Phase I/IIa
Methodology	This is an open label clinical trial. Patients with the HLA-A*0201, HLA-A*0205, and/or HLA-A*0206 allele and whose tumor expresses the NY-ESO-1 tumor antigen will be eligible to receive NY-ESO-1^{c259}T. The trial is conducted entirely with outpatient procedures; however, patients may be hospitalized for the cytoreductive chemotherapy at the discretion of the investigator. Upon enrollment, patients will undergo leukapheresis for T cell collection, and their cells will be genetically engineered and expanded ex vivo. Seven days prior to receiving T-cells patients will undergo a fludarabine/cyclophosphamide conditioning regimen to potentiate the immunotherapy. The cell product will be infused as a single infusion. Patients will be followed daily for the first week, weekly until 4 weeks, 8 weeks, and 12 weeks and then every 3 months until progression. Patients will undergo disease monitoring by MRI/CT scan (as appropriate for disease) at baseline, day 28, 8 weeks and 12 weeks, and then every 3 months thereafter until progression. Tumor biopsies will be taken at baseline, at week 8, and upon progression, as indicated. In patients who have progressive disease following initial infusion but whose tumors continue to express NY-ESO-1, these patients may be eligible for a second infusion with redirected T cells. At progression, the interventional portion of the protocol ends and long term follow-up (LTFU) continues, in accordance with FDA regulations. LTFU occurs semiannually for up to 5 years post infusion and then annually thereafter for up to 15 years.
Study Duration	In this trial, patients are restricted by HLA type and tumor antigen expression. Due to the rarity of this population of patients, we expect enrollment to be complete in approximately 3 years.
Study Center(s)	This is a multicenter trial.
Objectives	The primary objective is to evaluate the safety and tolerability of autologous genetically modified T cells transduced to express the high affinity NY-ESO-1^{c259} TCR in HLA-A*0201, A*0205, and/or A*0206 subjects. Secondary study objectives are: 1) To evaluate the effect of NY-ESO-1 $^{c\ 259}$T on tumor activity a, 2) to evaluate the persistence of genetically modified cells in the body and correlate with dose 3) evaluate the phenotype and functionality of genetically modified cells isolated from peripheral blood or tumor post infusion, 4) evaluate NY-ESO-1 expression in tumor tissue, before treatment, and correlate with results from archival tumor tissue, and

	5) evaluate NY-ESO-1 expression in tumor tissue, before and after treatment, and correlate with clinical response to treatment.
Number of Subjects	The target enrollment for this trial—across sites--is approximately 18 patients with at least 10 patients receiving fludarabine/cyclophosphamide conditioning
Diagnosis and Main Inclusion Criteria	Patients must have a diagnosis of recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma with refractory or platinum resistant disease and/or have received ≥ 2 lines of chemotherapy. Patients must be HLA-A*0201, A*0205, and/or A*0206, and have expression of NY-ESO-1 in their tumor as determined by IHC. Patients must have a life expectancy of > 4 months, be ECOG ≤ 1, have measurable disease as defined by RECIST, be able to undergo apheresis, and have normal organ and marrow function.
Study Product, Dose, Route, Regimen	The study drug in this protocol is NY-ESO-1^{c259}T and will be manufactured at a central manufacturing site. Patients will receive NY-ESO-1^{c259}T within the range of $1x10^9$ - $6x10^9$ transduced cells by gravity flow intravenous (IV) infusion.
Duration of administration	The infusion will take approximately 15-30 minutes, and patients will be followed in the clinic for at least 4 hours post infusion.
Statistical Methodology	With respect to the primary objectives and endpoints, no specific statistical hypotheses are being evaluated. All analyses will be descriptive and exploratory.

1 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

1.1.1 Recurrent Ovarian Cancer

[Excerpted from version 2.2011 of the National Comprehensive Cancer Network (NCCN) Guidelines: http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf].

Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 80%) (Chan, Cheung et al. 2006). Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and the country's fifth most common cause of cancer mortality in women. In the year 2010, there will be an estimated 21,900 new diagnoses and an estimated 13,900 deaths from this neoplasm in the United States; less than 40% of women with ovarian cancer are cured (Jemal, Siegel et al. 2009; Jemal, Siegel et al. 2010). The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life, with a rate of 57/100,000 women. The median age at the time of diagnosis is 63 years, and 70% of patients present with advanced disease (Fleming GF 2009).

Ovarian cancer is classified primarily as Stages I - IV. Since 1997, no significant changes have been made in the staging systems for ovarian cancer (Edge SB 2010). Pathologic grading continues to be an important prognostic factor and is used in the selection of therapy, primarily for early-stage disease. Grading is labeled as 1, 2, or 3. Except for those women with Stage I, Grade 1 tumors (in whom survival is greater than 95% after comprehensive laparotomy), patients in all other stages of ovarian cancer should be encouraged to enter clinical trials for both primary and recurrence therapy.

Due to the cryptic location of the ovary in the body and the asymptomatic nature of early stage ovarian cancer, the majority (63%) of patients are diagnosed with ovarian cancer after distant metastases have formed (http://www.seer.cancer.gov/statfacts/html/ovary.html). New therapies are greatly needed to address the unmet medical need of patients with refractory or resistant metastatic ovarian cancer.

Patients who have refractory or platinum resistant disease and/or have received ≥ 2 lines of chemotherapy are targeted for this clinical trial. Overall, the prognosis is poor (1) for patients who progress after 2 chemotherapy regimens without sustaining a clinical benefit (refractory); or (2) for those whose disease recurs in less than 6 months (platinum resistant). Note that progression in clinical studies of new therapies is typically defined using traditional RECIST (Response Evaluation Criteria in Solid Tumor) criteria (i.e., a 20% increase in tumor diameter) (Therasse, Arbuck et al. 2000), and more recently for immunotherapies by the Immune-related Response Criteria (irRC) for immunotherapies (Wolchok, Hoos et al. 2009). [NCCN] Panel members emphasized the importance of clinical trials to identify agents active

in this group of patients. Because these patients were resistant to their primary induction regimen, retreatment with a platinum compound is not generally recommended.

1.1.2 Redirected T Cell Therapy for Ovarian Cancer

Ovarian cancer is an ideal candidate for immunotherapy, and for an overview of immunotherapy in general for this disease, the following reviews are recommended (Kandalaft, Singh et al. 2010; Liu, Nash et al. 2010). The first data clearly indicating a relationship between tumor immunity and ovarian patient outcomes was the landmark paper by Coukos and colleagues which reported that the presence of TILs, detected by immunohistochemistry in tissue from 186 patients, in the primary tumor strongly correlated with patient survival (Zhang, Conejo-Garcia et al. 2003). The 5 year survival rate was 38% versus 4.5% in patients with or without TILs, respectively. These findings were strengthened by a subsequent report by Odunsi and colleagues that evaluated infiltrating T cell subsets (CD3/4/8 and CD25/FOXP3) in tissue from 117 patients. This study demonstrated that a CD8/4 ratio of approximately 2 or higher was correlated with improved survival time (Sato, Olson et al. 2005). The role of Tregs in poor prognosis would explain this ratio effect, and while staining for CD25/FOXP3 was suggestive in the study, it was not statistically significant. However, the inverse correlation between Treg infiltration in tumor and survival has been elegantly described by Zou and colleagues (Curiel, Coukos et al. 2004). In this study, Treg content was evaluated by flow cytometry (in ascites) or by multicolor confocal microscopy (in solid tumor); *in vitro* culture assays showed the Treg cells isolated from ascites or tumor were shown to be as suppressive as Treg from peripheral blood, confirming the suppressive phenotype of the cells. In 70 subjects, the quantitative Treg data was evaluated for correlation with clinical and pathological information (including survival). There was a significant inverse correlation between Treg content and survival, as well as a positive correlation with disease stage. Taken together these three studies strongly support the use of T cell immunotherapy for ovarian cancer, and in particular using clinical and manufacturing methods that reduce, to the extent possible, any contribution of Treg cells.

Initial studies demonstrating the potential of T cell immunotherapy to eradicate solid tumors came from the National Cancer Institute (NCI) in studies of adoptive transfer of *in vitro* selected tumor infiltrating lymphocytes (Dudley, Wunderlich et al. 2002; Dudley, Wunderlich et al. 2005). In these studies, 35 patients were treated with autologous TILs after lymphodepleting conditioning, and with concomitant IL-2. 18 patients (50%) had an objective response to the treatment, at times with large bulky tumors disappearing. The method of isolating and manufacturing TILs is labor intensive and only successful in a subset of patients (approximately 30% - 40%) (Dudley, Wunderlich et al. 2003). Therefore, the ability to genetically engineer tumor specific lymphocytes is an attractive alternative to reach greater numbers of patients, and patients with non-bulky disease.

One way to redirect a patient's own T cells to a specific tumor antigen is to genetically alter the cells to express a tumor antigen specific tumor cell receptor (TCR). Several studies have been opened for TCR redirected T cells to date, and are at various stages of completion. Two studies (Morgan, Dudley et al. 2006; Johnson, Morgan et al. 2009) evaluated three different TCRs isolated from tumor infiltrating lymphocytes, and chosen based on medium or high affinity binding to HLA-peptide complexes (Johnson, Heemskerk et al. 2006). In the first trial evaluating medium affinity MART-1 DMF4 TCRs, 31 patients were

reported. Subjects received as high as 8.6 x 10^{10} antigen specific redirected T cells. No toxicity related to T cell infusions was reported. Objective response rates in these trials were lower than observed in the TIL trials, with only 4/31 (13%) patients responding. In the follow-on trial utilizing the high affinity MART-1 DMF5 TCR or the gp100 TCR, a modestly higher objective response rate was observed of 30% (6/20) and 19% (3/16), respectively, with concomitant on target off tumor toxicity against the MART-1 or gp100 antigens causing reversible erythematous skin rash, uveitis and ototoxicity (Johnson, Morgan et al. 2009).

The lower response rate compared to the TIL trials may in part be due to the low affinity of naturally isolated TCRs against self-antigens. The central problem is tolerance: the repertoire of TCRs is generally of too low avidity to efficiently recognize tumor antigens, and this explains the failure of most cancer vaccines (Greenberg and Riddell 1999; Pardoll and Allison 2004; Rosenberg, Yang et al. 2004). Higher affinity recognition allows T cells to respond to lower levels of antigen; this is critically important for tumor immunotherapy where the tumor microenvironment has adapted itself to reduce expression of antigen and also decrease expression of MHC class I molecules (Marincola, Jaffee et al. 2000; Barrett and Blazar 2009). To address this problem, Adaptimmune developed a method for high throughput generation and analysis of TCRs mutated for higher affinity (Li, Moysey et al. 2005; Dunn, Rizkallah et al. 2006). One of these TCRs was derived from the 1G4, a clone specific for NY-ESO-1. In validation experiments performed in collaboration with the NCI, the NY-ESO-1^{C259} TCR was described (Robbins, Li et al. 2008). Of note, NY-ESO-1 is a cancer testes (CT) antigen that is less likely to induce on target off tumor toxicity due to its restricted expression (more on CT antigens below). This TCR subsequently was taken into a clinical trial by the Rosenberg team using a similar trial and manufacturing design as used for the TCR trials described above, in patients with melanoma or synovial sarcoma (Robbins, Morgan et al. 2011). The trial demonstrated safety and improved objective response rates using this TCR (5/11 in melanoma and 4/6 in synovial sarcoma). Notably, this is the same TCR as will be used in this trial, and there are several differences in manufacturing from the NCI trial, which may improve response rates.

In summary, ovarian cancer is an immunogenic cancer that is a reasonable target for T cell based immunotherapy. Previous trials using adoptive T cell therapy suggest promise for this approach in solid tumors.

1.1.3 Rationale for Targeting Cancer Testes Antigens

For a tumor antigen to be effective it must 1) be expressed on tumor but have limited to no expression on normal adult tissue, 2) serve a critical function to the tumor cell so that targeting the antigen is less likely to lead to tumor escape, and 3) be immunogenic so that it is capable of triggering an immune response. Cancer testes (CT) antigens are defined as proteins which are expressed in tumor cells and testes, but not expressed in more than 2 non-germline tissues (Simpson, Caballero et al. 2005). These genes are commonly expressed in the germline and during gametogenesis, and their core function during this process, e.g., cell immortalization, migration, and implantation, is thought to play a parallel role in the tumorigenesis process. CT antigens often have heterogeneous expression in tumors (Jungbluth, Busam et al. 2000) (Crystal Mackall, personal communication) which some believe may be a result of differential expression on cancer stem cells versus differentiated tumor cells.

CT antigens were first discovered in the late 1980's, in a melanoma patient who had an unexpectedly positive clinical course. The T cells from this patient recognized autologous tumor (Knuth, Wolfel et al. 1989), and further characterization of the CTLs resulted in discovery of the MAGE-A1, MAGE-A2, and MAGE-A3 genes (Traversari, van der Bruggen et al. 1992) (van der Bruggen, Traversari et al. 1991). There are at least 44 CT antigens that have now been described using autologous typing and later SELEX, which identified NY-ESO-1 (Chen, Scanlan et al. 1997; Simpson, Caballero et al. 2005).

CT antigens are mainly categorized into CTX, or those located on the X chromosome, and non-X CT antigens, which are distributed around the genome. About half the CT antigens are CT-X antigens and NY-ESO-1 antigens is in this group. CT-X antigens are often coexpressed (Sahin, Tureci et al. 1998) (Tajima, Obata et al. 2003), and this may be due to the global hypomethylation that accompanies expression (Kaneda, Tsukamoto et al. 2004). The frequency of CT antigen expression tends to increase with cancer stage.

The immunogenicity of the NY-ESO-1 antigen has been robustly established. Briefly, CT antigens have primarily been identified by using serum from patients to identify tumor specific targets, and thus selected by their ability to elicit immunity. NY-ESO-1 vaccine trials have demonstrated the ability of these proteins to generate a T cell response (Baumgaertner, Rufer et al. 2006). NY-ESO-1 has been extensively tested as an immunogen in cancer vaccine studies (summarized in Section 1.1.4), and NY-ESO-1 specific T cells have been administered in adoptive T cell studies and shown anti-tumor effects (Hunder, Wallen et al. 2008; Robbins, Morgan et al. 2011).

1.1.4 Previous Clinical Studies with NY-ESO-1 Vaccines

In the first human study of NY-ESO-1 vaccination, ESO157–165 peptide in conjunction with granulocyte/macrophage colony-stimulating factor was shown to induce HLA-A2-restricted $CD8^+$ T cell responses in patients without preexisting NY-ESO-1 immunity, although these peptide-induced $CD8^+$ T cell responses were generally of low affinity and did not recognize naturally processed NY-ESO-1 (Dutoit, Taub et al. 2002). Subsequently, recombinant NY-ESO-1 protein in a saponin-based adjuvant (ISCOMATRIX) was used to immunize Stage III and Stage IV melanoma patients after tumor resection (Maraskovsky, Sjölander et al. 2004). More recently, patients with a range of tumor types were immunized with recombinant vaccinia NY-ESO-1 and recombinant fowlpox NY-ESO-1 (Jäger, Karbach et al. 2006)(15), and recombinant protein with CpG adjuvant (Valmori, Souleimanian et al. 2007). These vaccine strategies were found to be safe, and induced high-titered NY-ESO-1 Ab, $CD4^+$, and $CD8^+$ T-cell responses in a high proportion of patients.

A number of studies targeting NY-ESO-1 in ovarian cancer patients have been conducted at Roswell Park Cancer Institute. Protocol RP02-28, a Phase I clinical trial of immunization with an NY-ESO-1 derived long peptide of dual MHC Class I specificities, mixed with incomplete Freund's adjuvant (Montanide ISA51) in 18 ovarian cancer patients (Odunsi, Qian et al. 2007). Protocol I 13303, a Phase II clinical trial of recombinant vaccinia-NY-ESO-1 (rV-NY-ESO-1) and recombinant fowlpox-NY-ESO-1 (rF-NY-ESO-1) in ovarian cancer patients whose tumors express NY-ESO-1 or LAGE-1. One serious adverse event (SAE) was reported to be unlikely due to rV-NY-ESO-1 or rF-NY-ESO-1. Toxicity and immunological results are

currently being evaluated. Protocol I27008 is an on-going Phase I study testing epigenetic modulation of NY-ESO-1 with 5-Azacytidine in combination with recombinant NY-ESO-1 protein admixed with GMCSF and IFA in ovarian cancer patients receiving liposomal doxorubicin for recurrent disease. Nine out of 12 planned patients have been enrolled; and no treatment related Grade 3 AEs have been noted. Protocol I 125207, a Phase I study testing recombinant canarypox expressing NY-ESO-1 and a triad of co-stimulatory molecules (TRICOM). Planned accrual of 12 patients has been completed and no Grade 3 toxicities attributable to the vaccine were noted. Our collective experiences from these studies indicate that NY-ESO-1 vaccines are safe. Moreover, NY-ESO-1 specific antibody responses and/or $CD8^+$ and $CD4^+$ T-cell responses were induced by vaccinations in a high proportion of patients. Vaccine-induced $CD8^+$ and $CD4^+$ T cell clones were shown to recognize NY-ESO-1 -expressing tumor targets. However, the relatively low frequencies of vaccine induced T cells might limit the clinical efficacy of all of these vaccine approaches.

The current study will seek to improve the efficacy of T cells targeting NY-ESO-1 by the use of redirected T cell therapy in order to promote durable tumor control.

1.1.5 Rationale for NY-ESO-1 Threshold

The threshold for NY-ESO-1 positivity ($\geq$50% of cells expressing 2+ or 3+) was initially established to mirror the threshold used in the first studies with NY-ESO-1 (Robbins, Li et al. 2008). When these studies were initiated a lower expression threshold was not explored. Currently, anti-tumor activity is being evaluated in patients with lower NY-ESO-1 expression (>1% of tumor cells expressing ≥ 1% and <50% of cells expressing 2+ or 3+) in Cohort 2 of the synovial sarcoma pilot study (ongoing study ADP-04511). Preliminary anti-tumor activity (Partial Response) has been observed in 4 patients with low expression in the synovial sarcoma. NY-ESO expression in tumor cells for these patients is as follows:

- 50% 1+, 20% 2+, 10% 3+
- 10% 1+, 20% 2+, 20% 3+
- 5% 1+, 5% 2+, 5% 3+
- 90% 1+

Review of recent data has led to the lowering of the threshold for NY-ESO-1 positivity to $\geq$10% of cells expressing 1+ in newly initiated studies at Adaptimmune and supports exploring this lower threshold in this ovarian cancer study. In addition, the NY-ESO-1 Clinical Trial Assay has undergone extensive good laboratory practice and CLIA validation to establish the sensitivity, specificity and performance (i.e. precision and reproducibility) of the assay. Further, the central laboratory director and lead pathologist who scores all NY-ESO-1 stained tumors across all Adaptimmune clinical trials has confirmed that the Sigma NY-ESO-1 primary antibody has not shown any non-specific staining of tumor cells. The negative controls support this. >10% tumor staining of 1+ intensity or greater is indicative of the presence of NY-ESO-1.

1.1.6 Rationale for Preconditioning with Chemotherapy

Following intensive animal and clinical research over the past decade, it is now generally accepted that the incorporation of lymphodepletion prior to adoptive T cell therapy enhances immune reconstitution by the transferred cells, and increases tumor specific responses. Immune reconstitution is enhanced through homeostatic proliferation of T cells which is different from antigen driven T cell expansion in that it occurs in the absence of costimulation (Ernst, Lee et al. 1999; Prlic, Blazar et al. 2001). Homeostatic proliferation is promoted by an increase in availability of γ-chain cytokines IL-7, IL-15, and IL-21 (Wrzesinski and Restifo 2005; Rapoport, Stadtmauer et al. 2009; Wallen, Thompson et al. 2009), and also by MHC-peptide interactions against self or tumor antigens (Ernst, Lee et al. 1999; Wrzesinski and Restifo 2005).

Lymphodepletion also enhances the activity of the adoptively transferred cells via the removal of inhibitory factors and activation of antigen presenting cells. It has been well modeled in mice that regulatory T cells have the ability to inhibit anti-tumor T cell responses (Shimizu, Yamazaki et al. 1999; Casares, Arribillaga et al. 2003). In humans, regulatory T cells have been clearly shown to be correlated with poor outcomes in ovarian cancer patients and to predict poor survival (Curiel, Coukos et al. 2004). Furthermore, chemotherapy activates antigen presenting cells through the induction of inflammatory cytokines and induction of tumor apoptosis and resulting cross presentation of tumor antigens to T cells, although the induction of cytokines by cyclophosphamide alone is minimal compared to regimens containing irradiation (Xun, Thompson et al. 1994; Chernysheva, Kirou et al. 2002).

The most common lymphodepletion regimens used in adoptive T cell therapy trials for solid tumors to date have incorporated cyclophosphamide and fludarabine (Dudley, Wunderlich et al. 2002; Dudley, Wunderlich et al. 2005; Johnson, Morgan et al. 2009; Robbins, Morgan et al. 2011). The use of cyclophosphamide alone can achieve lymphodepletion without long term immunosuppressive side effects, and has previously been used in combination with immunotherapy for ovarian cancer (Windbichler, Hausmaninger et al. 2000). Therefore, in this trial, cyclophosphamide alone was initially chosen for preconditioning.

Recent studies in lymphoma, chronic leukemia and acute leukemia using a chimeric antigen receptor showed increased CD4+ and CD8+ CAR-T cell expansion, persistence and disease-free survival when fludarabine was added in to a previously cyclophosphamide-only preparative regimen (Turtle et al, 2015). The cyclophosphamide was administered at 30 – 60 mg/kg x 1 day and fludarabine at 25 mg/m2/day x 3 – 5 days. A recent review by Batlevi et. al included a summary of lymphodepletion regimens with CD19 CAR-T. A variety of lymphodepleting regimens including cyclophosphamide alone, cyclophosphamide plus fludarabine, cyclophosphamide plus fludarabine plus other agents have been used and shown to be effective. The doses and schedule of cyclophosphamide and fludarabine have varied across these studies ranging from lower to higher doses of these agents. (Batlevi 2016).

The lymphodepleting regimen in which objective tumor responses have been observed in an ongoing Adaptimmune clinical study in synovial sarcoma uses a cyclophosphamide dose of 1800 mg/m^2/day for 2 days, in addition to fludarabine 30 mg/m^2/day for 4 days (ADP-04511).

Six subjects treated at the time of this Amendment in this ovarian cancer study (ADP-0011-001) have received cyclophosphamide alone for lymphodepletion at a range of doses. Persistence of gene-marked T cells have been suboptimal in these subjects. Circulating gene modified T cell persistence was short; 4 of 6 subjects had <1,000 copies/µg gDNA only 4 weeks post T cell infusion. Objective tumor responses have not been observed in the subjects with ovarian cancer. Based on the emerging data that the addition of fludarabine to cyclophosphamide may play a role in homeostatic expansion, potentially leading to improved efficacy of NY-ESO-1 T in patients with ovarian cancer. At least 10 subjects with cyclophosphamide and fludarabine to further explore the potential impact of combination lymphodepleting chemotherapy.

1.2 Investigational Agents

The investigational agent in this protocol is autologous CD4 and CD8 T cells, expressing a high affinity TCR specific for NY-ESO-1. This agent is called NY-ESO-1^{c259}T. This agent is on file with the FDA under IND (14603). The generation of each of the NYESO TCR along with some information on the lentiviral vector used and the cell manufacturing method are provided below.

1.3 Preclinical Data

The Investigator's Brochure contains detailed information about existing nonclinical experience with NY-ESO-1^{c259}T.

1.4 Clinical Data to Date

1.4.1 Prior Human Experience with NY-ESO-1^{c259}T

The Investigator's Brochure contains detailed information about clinical experience with NY-ESO-1^{c259}T.

1.4.2 Study Progress

As of January 2017, 8 patients have been enrolled on this study. The first patient treated in this study with pre-conditioning chemotherapy of cyclophosphamide 60 mg/kg/day for 2 days experienced a strong immunological response with a significant proliferation of the engineered T cells and symptoms of grade 3 cytokine release syndrome (CRS) which was treated with high dose steroids that abrogated the engineered T-cell function. Following a dose de-escalation of the pre-conditioning chemotherapy (cyclophosphamide 30 mg/kg/day for 2 days) the next four patients did not experience a response so the dose was increased (cyclophosphamide 1800mg/m^2/day for 2 days). Two patients were enrolled but unable to receive the NY-ESO-1^{c259}T cell infusion. One patient was treated under the cyclophosphamide 1800mg/m^2/day for 2 days pre-conditioning regimen and experienced Grade 2 CRS which resolved with

supportive therapy without the use of steroids or tocilizumab. This patient's best response was stable disease at Week 8, however was determined to have clinical progression at Week 10. No objective responses (CR or PR) have been reported. The current lymphodepletion regimen consists of fludarabine 30 mg/m^2/day x3 days and Cyclophosphamide 600 mg/m^2/day x3 days and to date no subjects have been treated under this regimen.

1.5 T-cell Dose Rationale

NY-ESO-1^{c259}T will be administered by a single, gravity flow IV infusion. Patients will receive NY-ESO-1^{c259}T within the range of 1x10^9 (1 billion) transduced cells to 6 x 10^9 (6 billion) transduced cells. For patients whose cells fail to meet the minimum cell dose requirement (1x10^9 transduced cells) during the manufacturing process, manufacturing of additional transduced T-cells from excess banked leukapheresis product will be undertaken to achieve a total dose in the target range. In the event that no banked leukapheresis product is available a second leukapheresis may be performed to achieve a dose in the target range. Patients that are enrolled but do not receive NY-ESO-1^{c259}T cells will be replaced.

Published studies have evaluated broad ranges of cell doses. Information to date indicates T cell therapy has been used up to doses of ~100 x 10^9 cells (Robbins, Morgan et al. 2011)) although the actual products used may differ depending on manufacturing methods. Activity seems to be indirectly related to dose administered (depending also on cell expansion and persistence) although high T cell doses may be associated with an increased risk of adverse events (e.g. cytokine release) and, conversely, doses as low as 0.015 x 10^9 (15 million) cells may be effective (Kalos, Levine et al. 2011). The initial dose for this trial was chosen based on published data, (Robbins, Morgan et al. 2011; Morgan, Dudley et al. 2006; Johnson, Morgan et al. 2009), and data supported by our related ongoing studies in myeloma and synovial sarcoma (described above in the IB). In general, adoptive transfer of autologous T cells is safe and well tolerated.

Current experience with NY-ESO-1^{c259}T (n=53 subjects treated as of January 2016) is with total cell doses in the range of 0.4 x 10^9 – 3.47 x 10^{10} with a transduction level of ~18 – 78% (transduced cell dose range of 0.23 x 10^9 – 14.36 x 10^9). No untoward adverse events have been observed in subjects who received higher transduced cell doses (>5 x 10^9 cells). Of the 5 subject who received <1 x 10^9 transduced cells, 3 subjects had poor expansion and persistence of transduced cells; meaningful clinical responses were not observed in 4 of the 5 subjects. No clear dose response relationship has been observed to-date.

2 OBJECTIVES

This study is designed to assess the safety and antitumor effects of NY-ESO-1^{c259}T in patients with treatment resistant or refractory metastatic ovarian cancer. While this study is not powered to detect efficacy, the results from this study will be used to establish the sample size necessary to power a follow-on Phase II study designed to determine the antitumor efficacy of NY-ESO-1^{c259}T.

2.1 Primary Objectives

To evaluate the safety and tolerability of autologous, genetically modified T cells transduced to express the high affinity NY-ESO-1^{c259} TCR in HLA-A*0201, A*0205 and/or A*0206 subjects.

2.2 Secondary Objectives

- To evaluate the effect of NY-ESO-1^{c259}T on anti-tumor activity**.**
- To evaluate the persistence of genetically modified cells in the body and correlate with dose.
- To evaluate the phenotype and functionality of genetically modified cells isolated from peripheral blood or tumor post infusion.
- To evaluate NY-ESO-1 expression in tumor tissue, before treatment, and correlate with results from archival tumor tissue.
- To evaluate NY-ESO-1 expression in tumor tissue, before and after treatment, and correlate with clinical response to treatment.

2.3 Exploratory Objectives

- Evaluate candidate biomarkers in tumor tissue and in blood samples and correlate with clinical response to treatment.
- To evaluate candidate biomarkers in liquid biopsies (peripheral blood plasma) as a surrogate to those from tumor biopsies.
- To evaluate candidate biomarkers in ascites fluid and correlate with clinical response to treatment.

2.4 Study Design

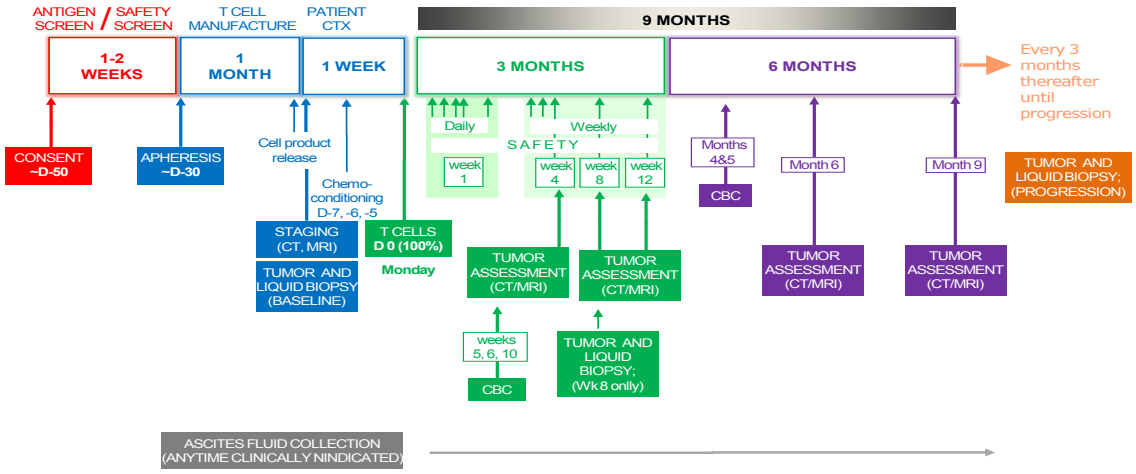
2.4.1 General Design

This is an open label clinical trial. HLA-A*0201, HLA-A*0205, and/or HLA-A*0206-positive patients whose tumor has been confirmed for expression of NY-ESO-1 will be enrolled in the study providing they meet the remaining eligibility criteria as summarized below. Eligible patients will have recurrent epithelial

ovarian, primary peritoneal or fallopian tube carcinoma with refractory or platinum resistant disease and/or have received ≥ 2 lines of chemotherapy. The trial is conducted entirely with outpatient procedures; however, patients may be hospitalized for the cytoreductive chemotherapy per investigator's discretion. Upon enrollment, patients will undergo leukapheresis for T cell collection, and their cells will be genetically engineered and expanded ex vivo. Seven days prior to receiving cells (recommend Monday), patients will start a fludarabine/cyclophosphamide conditioning regimen to potentiate the immunotherapy. Patients will receive the cell product as a single infusion (100% on Day 0; recommend Monday). Patients will be followed daily for the first week, weekly for 4 weeks, at 8 and 12 weeks, 6 months and every 3 months until disease progression. Additional CBCs will be collected at week 5, 6, 10, 16 and 20 for monitoring of recurrent pancytopenia. Patients will undergo disease monitoring by MRI/CT scan (as appropriate for disease) at baseline, 4 weeks, 8 weeks, 12 weeks, and at months 6, and 9 and every 3 months thereafter until progression.

Tumor biopsies and liquid biopsies will be taken at baseline, at Week 8, and upon progression and ascites fluid will be collected should there be a clinical need for removal at any time during the study. At disease progression, the interventional portion of the protocol ends and long term follow-up (LTFU) assessments continue, in accordance with FDA regulations. LTFU occurs semiannually beginning at progression until year 5 post infusion and then annually thereafter until year 15. The study schema is depicted in Figure 1.

Figure 1: Study Schema



2.4.2 Primary Study Endpoints

All adverse events will be recorded from the time of apheresis. All adverse events whether considered related or not will be recorded. This will include infusional toxicity, and any toxicity probably or definitely related to the NY-ESO-1^{c259}T including but not limited to:

- Fevers
- Rash
- Neutropenia, thrombocytopenia, anemia, marrow aplasia
- Hepatic dysfunction
- Pulmonary infiltrates or other pulmonary toxicity
- Development of GVHD

2.4.3 Secondary Study Endpoints

Secondary endpoints will evaluate correlates of treatment efficacy by measuring 1) clinical response rates to treatment and 2) the appearance of target antigen/MHC loss variants upon disease recurrence, as well as 3) immunological parameters associated with T cell persistence, bioactivity and functionality.

1. Clinical response rates to treatment: Tumor response is defined as CR, PR and SD for at least 4 weeks and PD. Clinical efficacy in terms of PFS, OS, BOR and Duration of Response will also be assessed. Patients will be followed for EFS until progression and for survival until death from any cause or loss to follow-up.

2. Appearance of target antigen/MHC loss variants upon disease recurrence will be evaluated, where available, by quantifying expression of targeted antigens/MHC alleles (NY-ESO-1/ HLA-A*0201/ A*0205/ A*0206) in tumor samples obtained on disease recurrence, and comparing those values to the pre-treatment (diagnosis) samples, as possible. NY-ESO-1 expression will be evaluated by Q-RT-PCR and/or immunohistochemistry. HLA expression on samples will be evaluated by immunohistochemistry.

3. Where available Immunological parameters associated with product bioactivity and functionality will measure selective migration and engraftment of gene-modified infused cells to the tumor post infusion, the ex-vivo immune functionality and phenotype of infused cells in tumor (where biopsies are safely accessible) and peripheral blood, the modulation of cytokine milieu in serum at baseline, and post T cell infusion as well as the development of an expanded patient immune response against tumor via epitope spreading.

2.4.4 Exploratory Endpoints

1. Candidate biomarkers will be analyzed from exosomes and cell-free DNA or plasma from subject's blood before and after T cell infusion and compared to those from tumor biopsies. Expression of these biomarkers will be correlated with treatment response

2. Candidate biomarkers will be analyzed from soluble and cellular components of the ascites before and after T cell infusion and compared to those from tumor biopsies. Expression of these biomarkers will be correlated to clinical treatment response

3 SUBJECT SELECTION AND WITHDRAWAL

For participation on this study, patients must meet all Inclusion/Exclusion criteria for enrollment (at screening) and at baseline (prior to chemotherapy).

3.1 Inclusion Criteria

To be included in this study, subjects must meet the following criteria:

1. Must have a diagnosis of recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma with refractory or platinum resistant disease and/or have received ≥ 2 lines of chemotherapy.
2. Age ≥ 18 years of age.
3. No significant immunodeficiency.
4. Have been informed of other treatment options.
5. Must be HLA-A*0201, HLA-A*0205, and/or HLA-A*0206 positive by high resolution testing.
6. Patient's tumor must be positive by histological assay for NY-ESO-1^{c259}T, according to the screening algorithm as described in Section 3.3. Positive expression,defined as ≥ 10% of cells that are 1+ by immunohistochemistry, is determine by pathological review at an Adaptimmune designated central laboratory.
7. ECOG performance status of 0 or 1. Refer to Table 4**.**
8. Life expectancy of > 4 months.
9. Prior therapies:

    a. Prior immunotherapy, monoclonal antibody therapy or prior investigational agents should be washed out 4 weeks before apheresis and must be completed 4 weeks prior to pre-infusion lymphodepletive chemotherapy.

    b. All previous cytotoxic chemotherapy, should be washed out 3 weeks before apheresis and must be completed at least 3 weeks prior to pre-infusion lymphodepletive chemotherapy.

    c. 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 lymphodepletive chemotherapy

    d. Biologic or other approved molecular targeted small molecule inhibitors should be washed out 1 week before apheresis and must be completed at least 1 week prior to pre-infusion lymphodepletive chemotherapy.

    e. Any grade 3 or 4 -hematologic toxicity of previous therapy must have resolved to grade 2 or less prior to apheresis and any grade 3 or 4 toxicity must have resolved to grade 2 or less prior to pre-infusion lymphodepletive chemotherapy.

f. All blood products transfused within 4 weeks prior to apheresis and within 4 weeks prior to pre-infusion lymphodepletive chemotherapy must be irradiated

10. Must have measurable disease as defined by RECIST 1.1.
11. Must have adequate venous access for apheresis.
12. Women of childbearing potential are requested to use acceptable methods of birth control for the duration of the study and until persistence of the study drug is no longer detected in the patient. This may be a period of several years. Methods for acceptable birth control include: condoms, diaphragm or cervical cap with spermicide, intrauterine device, and hormonal contraception. It is recommended that a combination of two methods be used.
13. Patients must have normal organ and marrow function as defined below:

- Leukocytes ≥ 3,000/mcL
- Absolute Neutrophil Count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Total bilirubin ≤ 1.5 ULN
- AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional upper limit of normal
- Creatinine clearance ≥ 50 ml/min
    - Patients <65 yrs of age can be assessed using estimated creatinine clearance calculated using the Cockcroft-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 Glomular Filtration Rate (GFR) measurement, according to standard practice at the treating institution.

14. Patient must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

3.2 Exclusion Criteria

Subjects will be excluded from this study for the following:

1. Currently receiving any other investigational agents.
2. Patients with active brain metastases. Patients with prior history of brain metastasis who have undergone local therapy (i.e., metastatectomy and/or radiation) and show no evidence of local recurrence or progression over the past 6 months are eligible.
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to fludarabine, cyclophosphamide or other agents used in the study.
4. Prior malignancy (except non-melanoma skin cancer) within 18 months of study entry.

NOTE: Patients must be in complete remission from prior malignancy in order to be eligible to enter the study.

5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Use of chronic corticosteroids, hydroxyurea, or immunomodulating agents (e.g., interleukin-2, interferon-alpha or gamma, granulocyte colony stimulating factors, etc.) within 30 days prior to study entry.

   NOTE: Recent or current use of inhaled steroids is not exclusionary. If subjects are prescribed a brief course of oral corticosteroids, the use should be limited to less than 7 days. Use of steroids before apheresis and immune assessment blood draws should be discouraged as it will affect white blood cell function.
7. Active infection with HIV, HBV, HCV, or HTLV as defined below, due to the immunosuppressive effects of cyclophosphamide used and the unknown risks associated with viral replication.
   - Positive serology for HIV.
   - Active hepatitis B infection as determined by test for hepatitis B surface antigen. Patients who are hepatitis B surface antigen negative but are hepatitis B core antibody positive must have undetectable hepatitis B DNA and receive prophylaxis against viral reactivation. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months
   - Active hepatitis C. Patients will be screened for HCV antibody. If the HCV antibody is positive, a screening HCV RNA by any RT-PCR or bDNA assay must be performed at screening by a local laboratory with a CLIA certification or its equivalent. Eligibility will be determined based on a negative screening value. The test is not required if documentation of a negative result of a HCV RNA test performed within 60 days prior to screening is provided.
   - Positive serology for HTLV 1 or 2
8. Receipt of an experimental vaccine within 2 months or in the opinion of the Investigator is responding to an experimental vaccine given within 6 months, or has received any previous gene therapy using an integrating vector.
9. History of severe autoimmune disease requiring steroids or other immunosuppressive treatments.
10. Lack of availability of a patient for immunological and clinical follow-up assessment.
11. Evidence or history of significant cardiac disease.

3.3 Subject Recruitment and Screening

This trial is posted on www.clinicaltrials.gov.

3.3.1 Number of Subjects and Duration of Study

The target enrollment for this trial is approximately 18 subjects. As of January 2017, 7 subjects have been enrolled in the initial cohort with cyclophosphamide alone as the cytoreductive chemotherapy for lymphodepletion (Cohort 1). With the approval of Protocol Version 6, sites began enrolling into a second cohort that administers fludarabine/cyclophosphamide cytoreductive chemotherapy for lymphodepletion. It is planned that at least 10 subjects will enroll in the second cohort to receive the fludarabine/ cyclophosphamide condition regimen (Cohort 2). As of January 2017 1 subject has been enrolled into Cohort 2. It is estimated that this study will take approximately 24 additional months to complete. The study will be considered complete once the last enrolled subject has transitioned to the long-term follow-up phase.

3.3.2 Sites

The protocol will be conducted in approximately 6 sites in North America. The number of centers is necessary to ensure recruitment in this targeted population. Additional centers may be added at the discretion of the Sponsor.

3.3.3 Method for Screening Subjects for HLA Alleles

NY-ESO-1^{c259} T specifically recognizes the HLA-A*0201, HLA-A*0205, and HLA-A*0206-restricted NY-ESO-1 peptide antigen HLA-A*02-SLLMWITQC; therefore, this protocol will select for subjects with these three HLA-A2 allelic variants and whose tumor expresses the NY ESO-1 antigen.
The prevalence of HLA sub-types varies from population to population. Information on the prevalence of HLA-A2 allelic variants in specific populations is available in the Allele Frequency Net Database (www.allelefrequencies.net). It is recommended that investigators review the database for HLA-A2 allelic variants relevant to the subject population at their site.

3.3.4 Method for Screening Subjects for Tumor Antigen

Patients' tumor will initially be screened for antigen expression by immunohistochemistry (IHC) for the NY-ESO-1^{c259}T antigen using archived or newly acquired formalin fixed paraffin embedded tissue. For patients to be determined to be NY-ESO-1^{c259}T positive, results will be reported via a central laboratory.

3.3.5 Screen Failures

A screen failure log documenting the investigators assessment of each screened patient with regard to the protocols inclusion and exclusion criteria is to be maintained by the investigator. Subjects who sign an informed consent form but do not meet eligibility criteria are defined as screen failures. For all screen failures, all screening data collected prior to the screen failure must be entered onto the database.

3.4 Early Withdrawal of Subjects

3.4.1 When and How to Withdraw Subjects

Subjects will be withdrawn from the study prior to the expected completion date for the following reasons:

- Unacceptable toxicity and other safety reasons that hinder completion of protocol specific procedures.
- Confirmed progression or disease relapses.
- Subject consent withdrawal.
- Decision by the investigators and/or Sponsor that withdrawing is in the patient's best interest.

Standard supportive therapy may be maintained for subjects withdrawn from active treatment. Every effort will be made to collect toxicity information on withdrawn patients.

4 STUDY DRUG

4.1 Description

The investigational agent in this protocol is autologous CD4 and CD8 T cells expressing a high affinity TCR specific for NY-ESO-1. This agent is called NY-ESO-1^{c259}T. The agents are on file with the FDA under individual IND 14603. The generation of the TCR, along with some information on the lentiviral vector used and the cell manufacturing methods are provided in **the IB**.

4.1.1 Cytoreductive Chemotherapy

Patients will begin infectious prophylaxis for pneumocystis carinii, herpes zoster and herpes simplex the day prior to commencing lymphodepletion, or as clinically indicated. Chemotherapy will be administered as indicated in the **Table 1.** Antiemetics and hydration for administration of chemotherapy will be given according to standard institutional practice.

Table 1: Regimen Description

<table>
<tr><td colspan="2">Regimen</td><td colspan="4">fludarabine + cyclophosphamide</td></tr>
<tr><td colspan="5">Conditioning</td><td>Recommended supportive medication</td></tr>
<tr><td>Day</td><td>Drug</td><td>Dose</td><td>Route</td><td>Administration[4]</td><td rowspan="11">Hydration: Ensure adequate hydration and antiemetic provision prior to commencing cyclophosphamide infusions

Mesna: may be given per institutional guidelines or as recommended in Section 4.1.3

G-CSF[3]: s/c daily from 24 hours post final cyclophosphamide

Cell therapy premedication: premedication should be given approximately 30 minutes prior to the NY-ESO1^{c259}T infusion as described in Section 4.1.4</td></tr>
<tr><td rowspan="2">-7</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</td><td>600 mg/m^2</td><td>IV</td><td>in 100 – 250 ml 0.9% NaCl over 1 hour</td></tr>
<tr><td rowspan="2">-6</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</td><td>600 mg/m^2</td><td>IV</td><td>in 100 – 250 ml 0.9% NaCl over 1 hour</td></tr>
<tr><td rowspan="2">-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></tr>
<tr><td>Cyclophosphamide</td><td>600 mg/m^2</td><td>IV</td><td>in 100 – 250 ml 0.9% NaCl over 1 hour</td></tr>
<tr><td>-4</td><td colspan="4">start G-CSF[3]</td></tr>
<tr><td>-3</td><td colspan="4"></td></tr>
<tr><td>-2</td><td colspan="4"></td></tr>
</table>

-1		
0	**NY-ESO1^{c259}T infusion$^{(2)}$**	

Notes:

1 Fludarabine dose will be adjusted in renal impairment as described in Section 4.1.2
2 Administration of NY-ESO1^{c259}T infusion is described in Section 4.1.4
3 Long-acting (pegylated) G-CSF may be given instead of short acting G-CSF according to institutional standard practice.
4 Or per institutional standards

4.1.2 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
50 – 79 mL/min	20 mg/m^2

4.1.3 Mesna

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.

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

4.1.4 NY-ESO-1^{c259}T T cell Administration

In the 5 initial patients enrolled under protocol versions prior to Version 5, NY-ESO-1^{c259}T was provided as target doses of 5 – 10 x 10^9 total cells, which were administered in a split infusion.

All patients enrolled under protocol Version 5 or later will be administered NY-ESO-1^{c259}T by a single 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 procedures.

Patients will receive at least 1x10^9 transduced cells, with a maximum possible dose of 6x10^9.

Treatment will be administered on an outpatient or inpatient basis, according to the investigator's discretion. Premedication with antihistamines and acetaminophen is recommended and may be given in accordance with institutional standards. Aspirin may be substituted for acetaminophen for patients allergic to acetaminophen. At the investigators' discretion, patients may be hospitalized for the cytoreductive chemotherapy and/ or T 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 15-30 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.

4.1.5 Second Infusion

Patients who have a clinical response to the first infusion and experience documented progressive disease will be eligible for a second T cell infusion with previously manufactured cell product (or from residual or gene modified T cell-negative apheresis product, or product from a second apheresis providing there is no persistence of gene modified cells detected prior to apheresis) for up to 6 months after confirmation of disease progression if their tumors are shown to continue to express the appropriate antigen target. Patients must also continue to meet study inclusion and exclusion criteria. The second infusion will be administered following the current protocol specified cytoreductive chemotherapy regimen.

4.2 Management of Toxicities and Complications

4.2.1 Infection

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

4.2.1.1 Cytomegalovirus

Subjects will be screened for cytomegalovirus (CMV) seropositivity at study entry. All CMV seropositive subjects will continue to be monitored for CMV viremia by CMV DNA PCR until 60 days post infusion of NY-ESO-1^{c259}T. In the event CMV viremia is observed an Infectious Diseases specialist should be consulted and treatment initiated if necessary according to institutional practice.

If a subject experiences prolonged or secondary pancytopenia or lymphopenia additional monitoring for viral reactivation should be considered and treatment for viral infection initiated if necessary. A strategy for management of pancytopenia or bone marrow failure is described in Section 4.2.8 .

4.2.1.2 Hepatitis B Prophylaxis

Subjects will be screened for hepatitis B (HBV) at study entry. Subjects who are hepatitis B core antibody positive must receive prophylaxis against viral reactivation using institutional protocols. Prophylaxis should be initiated prior to lymphodepleting therapy and continued for 6 months.

4.2.2 Hematologic and Blood Product Support

Blood product support should be provided to maintain platelets > 10 x10^9/L, Hb > 8.0 g/dL (or in accordance with the institutional practice) and as clinically indicated. See AABB Guideline on platelet transfusion [2015].

4.2.2.1 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 lymphodepleting chemotherapy and following lymphodepleting chemotherapy until at least 6 months following IP infusion or until lymphocyte count returns to ≥1.0 x10^9/L (whichever is longer) must be irradiated. In addition, if a subject requires systemic steroids or immunosuppression for the treatment of toxicity, irradiated blood products must be given until recovery of immune function

4.2.2.2 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 (i.e. both CMV-positive and -negative subjects) should receive leukoreduced blood products where possible (excluding the NY-ESO-1^{c259}T infusion). Where leukoreduced blood is not available, CMV negative subjects must only receive blood products from CMV-seronegative donors from study entry to study completion.

4.2.3 Management of Neutropenia using Filgrastim

Per ASCO guidelines for the management of neutropenia, filgrastim (G-CSF) should be given 24 hours after the administration of myelotoxic chemotherapy. G-CSF should be continued until reaching an absolute neutrophil count (ANC) of at least 2 to 3 × 10^9/L.

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

4.2.4 Management of Symptoms during T Cell Infusion

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

- Fever, chills and temperature elevations will be managed with acetaminophen. All subjects that develop fever or chills will have a blood culture drawn.
- Headaches may be managed with acetaminophen following a neurologic examination.
- Nausea, vomiting will be treated with a non-steroidal anti-emetic of choice.
- Hypotension will initially be managed by intravenous fluid administration and further measures as dictated by standard medical practice.
- Hypoxemia will initially be managed with supplemental oxygen and further measures as dictated by standard medical practice.

4.2.5 Management of Autoimmunity

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

4.2.6 Management 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, Gardner et al. 2014).

The recommended management of CRS depends on the grade, which has been further adapted from CTCAE for use with immunotherapy and should be implemented in accordance with institutional guidelines. Symptoms can mimic those seen with infection. The diagnosis of CRS is clinical, and is supported by the exclusion of infection as well as the presence of increased cytokine levels and other biomarkers. Assessment and treatment guidelines are provided below. If CRS is suspected, in addition to assessment for infection, cytokine levels as well CRP levels should be measured approximately every other day until symptoms are improving or an alternative diagnosis is confirmed.

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 one low dose pressor, hypoxia responds to <40% O_2, and/or Grade 2 organ toxicity)	• Monitor cardiac and other organ function • 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] 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 immunosuppressor agents may be used, including TNFα and IL-1R inhibitors

Source: Lee, 2014

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

Patients 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 due to the potential to inhibit the anti-tumor effects of the adoptive T-cell therapy.

However, in patients 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.

The product label for tocilizumab can be found at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125472s000lbl.pdf

Please note that labels are subject to change and the most current version of the label should be referenced if there are any questions.

4.2.7 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 [**Error! Reference source not found.Error! Reference source not found.**, 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 subjects with multiple myeloma. There is the potential for subjects who receive lymphodepleting therapy followed by engineered autologous T-Cell infusion to experience GVHD and/or autoimmune GVHD-like symptomatology. Autologous GVHD is typically milder than classic (allogeneic) GVHD [Kline, 2008], and is usually manageable with treatment. However, severe cases (including fatalities) have been reported [Fidler, 2012]. There are no published guidelines for the management of autologous GVHD. However, lessons can be drawn from published case reports and guidelines for the diagnosis and management of acute GVHD following allogeneic transplant [Dignan, 2012].

4.2.7.1 Diagnosis of GvHD

The diagnosis of GVHD is predominantly based on clinical findings and is often one of exclusion. Many of these symptoms can also occur in the setting of the preparative regimen, high dose cyclophosphamide as well as with 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 subjects following bone marrow transplant.

Bone marrow suppression is also a feature of transfusion-related GVHD. To minimize the possibility of transfusion-related GVHD, see Section 4.2.2.1for guidance on irradiated blood products.

4.2.7.2 Grading of GvHD

Grading of acute 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				

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

Otherwise, there are several additional second line treatment options for which there is currently limited and/or evolving supporting data. Treating physicians can refer to the Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and

Marrow Transplantation guideline for diagnosis and management of acute graft-versus-host disease [Dignan, 2012].

4.2.8 Management of Pancytopenia with Bone Marrow Failure/ Aplastic Anemia

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

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

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

Management of 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. Refer to Section 10 (Correlative Data Analysis). Details on tissue collections, kit use and shipment information can be found in the manual of procedures.
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 G-CSF
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/Infectious Diseases consultant(s). If high dose corticosteroids are initiated, continue for a minimum of 5 days and taper gradually with advice from expert consultants.

Refer to Section 4.2.7 (Management of Graft-versus-Host Disease) regarding bone marrow suppression as a feature of GVHD.

4.3 Prior and Concomitant Therapy

All prescription and nonprescription medication, vitamins, herbal and nutritional supplements, taken by the subject during the 30 days prior to screening will be recorded at the screening visit. All anti-cancer treatments taken by the subject must be recorded regardless of time. At every visit, concomitant medications will be recorded in the medical record and on the appropriate CRF. Any additions, deletions, or changes of these medications will be documented.

4.3.1 Active Infection

Active infections occurring after initiating the study should be treated according to the standard of care.

4.3.2 Disallowed Agents

The following treatments are prohibited on the study: Any other anti-cancer treatment including non-protocol surgery, non-protocol chemotherapy, immune therapy, biological therapy, or investigational anti-cancer therapy. Radiotherapy to target lesions or new lesions is not allowed.

The following agents are not allowed while on study: systemic corticosteroids (unless before cytoreductive therapy and except as outlined for management of CRS), immunotherapy (e.g., interleukins, interferons, other vaccines, intravenous immunoglobulin, expanded polyclonal TIL or LAK therapy), pentoxifylline, or other investigational agents due to their immunosuppressive or immunomodulatory effects on the study drug.

Patients who have not received the influenza vaccine prior to treatment on the protocol may receive the vaccine after they have normalized their blood counts.

4.4 Subject Compliance Monitoring

Informed consent must be obtained from all patients before entry into the study. The study team will monitor compliance with the protocol. Any steps in this sequence that are missed must be recorded as protocol violations.

4.5 Receiving, Storage, Dispensing and Return

4.5.1 Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

4.5.2 Storage

The final cell product is frozen and stored at the central manufacturing facility. Viability tests will be performed before releasing the cells for use. Cells will be shipped in a cryoshipper prior to infusion to the clinical site, where the cells will be removed from the shipper and stored in vapor phase liquid nitrogen or a mechanical freezer at $\leq$ -130 ^{o}C until the infusion day.

4.5.3 Return or Destruction of Study Drug

The study drug may require return to the manufacturing facility. Any unused study drug will be returned to the manufacturing facility at the discretion of the Sponsor.

5 STUDY PROCEDURES

5.1 Informed Consent and Study Enrollment Procedures

All subjects are required to sign a statement of informed consent prior to the conduct of any study-related procedures. This Phase I study involves research that presents risk, but holds the prospect of direct benefit to the individual subject (46.405-45 Code of the Federal Regulations part 46). It is the responsibility of the investigator to give each subject (or the subject's acceptable representative) prior to inclusion in the study, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The subjects must be informed about their rights to withdraw from the study at any time. Written subject information must be given to each subject before enrollment. Furthermore, it is the responsibility of the investigator to obtain signed ICF for all subjects prior to inclusion in the trial.

Upon enrollment, it is the responsibility of each investigator to provide to the Sponsor a completed enrollment form, and supporting documents providing proof of each eligibility criterion.

5.2 Screening and Baseline Evaluations

Patients will provide their written informed consent for HLA typing and antigen screening.

If the patient is eligible based on HLA type and tumor antigen expression, then the patient will undergo the remainder of the screening and baseline procedures according to Schedule of Procedures outlined in Table 2. Procedures include:

- Medical history and concomitant medications
- HLA and Tumor Antigen analysis (Screening)
- CT or MRI
- Targeted physical exam (height collected at screening only)
- Determination of performance status
- CBC and differential
- Ferritin (Screening)
- Complete metabolic and hepatic panel
- Baseline CA-125 reading (Screening)
- Urinalysis
    - Patients >65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement, according to standard practice at the treating institution.

- Uric Acid (Screening)
- Prothrombin time
- Screening for active viral infections (Screening)
- ECHO or MUGA (Screening)
- Troponin, EKG
- Collection of blood for research assessments (Baseline)
- Tumor and liquid biopsy (Baseline)
- Ascites fluid collection (if clinical need for removal of ascites fluid at any time on study)

5.3 Leukapheresis

After enrollment, the leukapheresis date will be scheduled based on the T cell manufacture schedule at the manufacturing facility. All patients will undergo an approximately 10 L – 12 L mononuclear cell apheresis procedure to collect steady-state T-cells. Antecubital veins will be used, or when necessary, a central catheter will be placed. A standard collection protocol will be used to obtain the peripheral white blood cells with settings modified to obtain the best mononuclear cell yield. In order to obtain sufficient cells, leukapheresis time may vary from 90 minutes to 240 minutes. The collection goal will be about 1×10^8 mononuclear cells/kg body weight. The minimum collection will be set a 1.5×10^7 mononuclear cells/kg. However, if the minimum collection is not reached, then a second apheresis procedure can be performed if recommended by the Sponsor. Cells will be transferred same day/overnight by courier to the manufacturing facility where they will be processed. Autologous leukapheresis product, counts, and recoveries will be monitored for each donation. The procedure will be performed according leukapheresis protocols at the study sites. Refer to Schedule of Procedures outlined in Table 2.

Requirements for reporting adverse events begin at the time the patient undergoes the leukapheresis procedure.

5.4 Baseline Imaging

Per eligibility criteria, patients must have measurable disease. A baseline CT scan (or MRI) of the chest, abdomen and pelvis, should be obtained within 7 days prior to initiation of cytoreductive chemotherapy. Lesions must be selected and size measurements recorded according RECIST v 1.1. Note: lesion size must be determined by anatomical imaging with CT or MRI. Size or activity (e.g. SUVmax) from PET alone (or other imaging techniques e.g. radioisotope bone scan) is not sufficient. Throughout the study, lesions must be assessed using the same technique as at baseline (CT or MRI). Refer to Schedule of Procedures outlined in Table 2.

5.5 Cytoreductive Chemotherapy

As described earlier in Section 4.1.1. Refer to Schedule of Procedures outlined in Table 2.

- Concomitant medications
- Adverse events
- Targeted physical exam
- Determination of performance status
- CBC and differential
- Complete metabolic and hepatic panel
- CA-125 monitoring
- Troponin/ EKG
- Ascites fluid collection (if clinical need for removal of ascites fluid at any time on study)

5.6 T Cell Infusion (Day 0)

It is recommended that T cell infusions occur typically on Monday (Day 0) for single infusions. T cell products will be shipped to the clinical sites in accordance with validated shipping procedures and SOPs. Refer to Schedule of Procedures outlined in Table 2.

- Concomitant medications
- Adverse events
- Determination of performance status
- CBC and differential
- Complete metabolic and hepatic panel
- Uric Acid
- Troponin, EKG
- CA-125 monitoring
- Collection of blood for research assessments (least 1 hour post-infusion)
- Weight (pre-infusion); vitals will be collected pre-infusion and 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours post infusion.
- Ascites fluid collection (if clinical need for removal of ascites fluid at any time on study)

5.7 Post Infusion Follow-up (Days 1-4 and Day 7)

Patients will be followed daily for Days 1-4 and also at Day 7 following the infusion. Refer to Schedule of Procedures outlined in Table 2. These visits will include the following procedures:

- Concomitant medications
- Adverse events
- Vital signs
- Determination of performance status
- CBC and differential
- Ferritin
- Complete metabolic and hepatic panel
- CA-125 reading
- Uric Acid
- Troponin/ EKG
- Collection of blood for research assessments
- Ascites fluid collection (if clinical need for removal of ascites fluid at any time on study)

5.8 Post Infusion Follow-Up (Weeks 2 - 4)

Starting with the second week, patients will be followed weekly until week 4. There is a ± 2 day window for these visits, which will include the following procedures. Refer to Schedule of Procedures outlined in Table 2.

- Concomitant medications
- Adverse events
- Targeted physical exam (Weeks 2 and 4)
- Vital signs (Week 3)
- Determination of performance status
- CBC and differential
- Ferritin (Weeks 2 and 4)
- Complete metabolic and hepatic panel
- CT/MRI

- CA-125 reading
- Uric Acid
- Collection of blood for research assessments
- Troponin/ EKG (Week 2)
- ECHO/MUGA (Week 4)
- Ascites fluid collection (if clinical need for removal of ascites fluid at any time on study)

5.9 Post Infusion Follow-Up (Weeks 5, 6, 10, 16, 20)

At Weeks 5, 6, 10, 16 and 20 (± 2 days), CBC (with differential) monitoring for the management of pancytopenia/aplastic anemia will be performed.

5.10 Post Infusion Follow-Up (Week 8 and Week 12)

Patients will be followed at Week 8 (± 2 days) and Week 12 (± 1 week). The reason for the smaller window at Week 8 is that this time point is important for staging and monitoring for adverse events. Refer to Schedule of Procedures outlined in Table 2. These visits will include the following procedures:

- Concomitant medication
- Adverse events
- Targeted physical exam
- Determination of performance status
- CBC and differential
- Complete metabolic and hepatic panel
- CA-125 reading
- Collection of blood for research assessments
- CT/MRI
- Ferritin (Week 8)
- Tumor and liquid biopsy (week 8)
- Ascites fluid collection (if clinical need for removal of ascites fluid at any time on study)

5.11 Post Infusion Follow-Up (6 Months and then every 3 months until disease progression)

Patients will be followed at 6 and 9 months (± 1 week) and then every 3 months until disease progression. Refer to Schedule of Procedures outlined in Table 2. These visits will include the following procedures:

- Concomitant medication
- Adverse events
- Targeted physical exam
- Determination of performance status
- CBC and differential
- Complete metabolic and hepatic panel
- CA-125 reading
- Collection of blood for research assessments
- CT/MRI
- Tumor and liquid biopsy (at progression)
- Ascites fluid collection (if clinical need for removal of ascites fluid at any time on study)

5.12 Long Term Follow-Up (Years 1 - 15)

Evaluations will be performed for up to 15 years on all subjects as specified by FDA, in accordance with recent guidelines for long term follow-up (LTFU) set forth by the ASGT and the FDA. Subjects may be rolled over to a LTFU protocol or subjects will continue to be followed as described in Table 2 and Appendix C.

Please refer to Table 2 and Appendix C for Long Term Follow-up.

The most recently released (November 2006) Guidance on Monitoring for Delayed Adverse Events states that for the first 5 years, all subjects should undergo monitoring of vector sequences every 6 months, and a full physical examination including a medical history, concomitant medications and examination of appropriate organ systems and a hemogram annually. For the final 10 years, if vector sequences are no longer detected in PBMCs, a one page questionnaire or post card may be sufficient for reporting of any adverse events and questions relating to the patient's status.

For the LTFU in this study:

- Subjects who have completed the 9 month visit, the first visit will occur at 1 year post T cell infusion and then every 6 months until the end of year 5 post T cell infusion.
- For subjects who do not complete the 3 month visit, the first visit will occur at 3 months post T cell infusion, the second visit will be 6 month post T cell infusion, the third visit will occur at 9

months post T cell infusion and the next visit will occur 1 year post T cell infusion, and then every 6 months until the end of year 5 post T cell infusion.

Visits will include a medical history, physical exam, and blood tests for disease monitoring, CBC, chemistries, monitoring for persistence of vector modified cells and annually for RCL testing/archive. The physical exam and medical history (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. See Appendix C: Long Term Follow Up.

For the next 10 years, subjects will be asked to return for testing only if vector modified cells were detected in the previous year, and if so, then blood for persistence of vector modified cells and RCL testing (archive) will also be performed/collected. If no vector modified cells were detected in the previous year, the follow-up will be conducted by means of a clinical questionnaire completed via phone or through the mail by the study coordinator. The questionnaire will include the following questions:

- When did you last visit your personal physician?
- Has there been a change in your condition? Are there any adverse events to report?
- Did you have a blood test?
- Did your physician express any concerns with the test results?

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 A: Sample Patient Letter for Long Term Follow-Up.

5.13 Requirements for a Tumor Biopsy

Screening Prior to Apheresis

Collection of a tumor biopsy at screening is only required if there is no archival tissue available to test for NY-ESO-1 positivity. If archival tissue (i.e. FFPE) is available, this can be used for screening purposes and a tumor biopsy would not be required.

Baseline and Week 8

Core needle tumor biopsies are required at baseline and Week 8, with the exception of patients for whom there is no safely accessible tumor tissue. If possible, biopsies should consist of multiple cores. The baseline biopsy material may be collected anytime between two months and 2 weeks prior to the start of chemotherapy, with a preference for the biopsy to be taken closer to the time of infusion. The tumor tissue should be taken from non-target lesions and when possible the same lesion(s) should be biopsied at both baseline and Week 8. If it is not possible to biopsy the same non-target lesion(s) at Week 8, 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 week 8 should be noted at the time (e.g. decreased, stable, increased size or activity).

Disease Progression

Biopsy material should be collected (with exception of patients for whom there is no safely accessible tumor) after disease progression has been confirmed and documented. Ideally the biopsy should occur on lesions that have progressed (or the same lesion(s) biopsied at Week 8 or another lesion in the same anatomical region) if possible.

Biopsy collection and sample preparation methods can be found in the Manual of Procedures.

5.14 Requirements for Liquid Biopsies

In all patients, at baseline, week 8 and at disease progression, we request a parallel blood collection for liquid biopsies. Liquid biopsies should be collected at the same time that tumor biopsies are requested.

It is preferable a tumor biopsy be collected if it is feasible and that the collection of a liquid biopsy be conducted in addition to the tumor biopsy and/or ascites, and should not substitute the collection of the tumor biopsy and/or ascites.

5.15 Requirements for Ascites Fluid Collection

Should there be a clinical requirement for removal of ascites fluid in a patient at any time on study, we request that a sample be collected for correlative research studies. This ascites sample is an additional collection and is not in place of any protocol specified biopsies.

6 SCHEDULE OF PROCEDURES AND OBSERVATIONS

The schedule of procedures and observations for this study is summarized in Table 2: Schedule of Procedures and Observations below.

Table 2: Schedule of Procedures and Observations

Schedule [8]	Screening 1	Screening 2	Leuka-pheresis	Baseline w/in 7 days prior to chemo	Chemo Infusion Day -7 Day -6 Day -5	T cell infusion Day 0 (Mon.)	Days 1-4	Day 7	Weeks 2-4 (weekly)	Week 8 (Weeks 5, 6, 10) [19]	Week 12 (Weeks 16, 20) [19]	Month 6 and every 3 months	At confirmation of PD	LTFU [14]	
														Years 1-5	Years 6-15
Procedures															
Cyclophosphamide and fludarabine[9]					X										
Apheresis			X												
T Cell Infusion						X [1]									
MRI/CT		X		X					X [17]	X	X	X	X		
Tumor Biopsy [3]	X			X						X			X		
Exosome and cfDNA collection (liquid biopsy)[3]				X						X			X		
Ascites Fluid Collection [3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]		
Clinical Assessments															
Informed Consent	X	X													
Medical History		X												X	X
Targeted Physical Exam		X		X	X	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X	X
ECOG Performance Status		X		X	X	X	X	X	X	X	X	X	X	X	X
CBC, differential		X		X	X	X	X	X	X	X	X	X	X	X	
Ferritin		X					X [15]		X [2]	X					
Complete Metabolic and Hepatic Panel		X		X	X	X	X	X	X	X	X	X	X	X	
Urinalysis		X[12]		X[12]											
Uric Acid		X				X	X	X	X						
Prothrombin Time		X		X											
Troponin/EKG		X		X	X	X [10]	X [10]	X[10]	X [16]						
ECHO or MUGA		X							X [17]						
HLA/ Tumor Antigen	X [11]														
HIV, HTLV 1/2, Hep B, Hep C, CMV IgG		X													
CA-125 Monitoring		X			X [5]	X	X	X	X	X	X	X	X		
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event			X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule [8]	Screening 1	Screening 2	Leuka-pheresis	Baseline w/in 7 days prior to chemo	Chemo Infusion Day -7 Day -6	T cell infusion Day 0 (Mon.)	Days 1-4	Day 7	Weeks 2-4 (weekly)	Week 8	Week 12	Month 6 and every 3 months	At confirmation of PD	LTFU [14]	
														Years 1-5	Years 6-15
Research Assessments															
Vector Copies (Persistence)				X		X [6]	X	X	X	X	X	X[18]	X	X	X
VSV-G DNA (RCL) [7]				X							X	X		X	X
PBMC (Functional Assays, Immunophenotyping)				X		X [6]	X	X	X	X	X	X	X		
Cytokine Analyses and Humoral Anti-Infused Cell Responses [13]				X		X [6]	X	X	X	X	X	X	X		

1. 100% of total dose given on day 0. Recommended day for infusion is Monday so that all procedures can be collected during business hours Monday-Friday.
2. Weeks 2 and 4 only.
3. Requirements for a tumor biopsy are described in Section 5.13; Requirements for liquid biopsy collection are described in Section 5.14. Requirement for ascites fluid collection are described in Section 5.15, Ascites fluid will be collected in patients who have an accumulation of ascites, should there be a clinical need for removal of the ascites fluid at any time on study.
4. On Day 0, vitals will be monitored prior to and at 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours and 4 hours post infusion. Pre-infusion weight will be collected. Vitals only will be collected on Days 0-7 and Week 3.
5. Taken pre-infusion.
6. Sample collected any time at least 1 hour post infusion.
7. If negative at 1 year then VSV-G sample can be archived in years 2 - 5 for look back analysis as needed.
8. Weekdays are shown because in most cases, due to the weekend, the patient procedures will fall on these days. However, the weekdays may be altered as needed. 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 7-10 days prior to leukapheresis for laboratory tests, and within four weeks prior to screening for ECHO/MUGA, or MRI/CT. Additional tests may be done at any time if clinically indicated.
9. At the investigators' discretion, patients may be hospitalized for the cytoreductive chemotherapy; Mesna administered in accordance with institutional standards; Patients will begin infectious prophylaxis for pneumocystis carinii, herpes zoster and herpes simplex the day prior to commencing preparative chemotherapy, or as clinically indicated; G-CSF should be given from 24 hours after the last dose of cyclophosphamide until resolution of neutropenia in accordance with ASCO guidelines or institutional practice. Long-acting (pegylated) G-CSF may be substituted according to institutional practice
10. Collected prior to infusion on Day 0, and Days 1- 4, and as clinically indicated after Day 4.
11. Patients eligible for second infusion must continue to meet eligibility for tumor antigen positivity.
12. Patients >65 years of age must have renal function measured either by 24-hour urine creatinine collection or by nuclear medicine EDTA GFR measurement
13. Humoral Anti-infused Cell Responses are collected as part of the cytokine analysis. Aliquots will be stored at a central vendor for potential analysis from baseline, Week 8, Month 6 timepoints and every 3 months thereafter.
14. Follow-up is required for patients that discontinue, see Appendix C: Long Term Follow Up for detailed list of procedures to be performed during long-term follow-up.
15. Day 4 only.
16. Week 2 only.

17. Week 4 only.
18. Month 6 persistence sample is collected for safety assessment
19. CBC (with differential) only will be collected at Weeks 5, 6, 10, 16, and 20 for monitoring of pancytopenia.

Table 3: Blood Volume for Research Assessments

Blood Collected for Research Assessments	Screening prior to apheresis	Leuka-pheresis	Baseline w/in 7 days prior to chemo	Chemo Infusion Day -7 Day -6	T cell infusion Day 0 (Mon.)	Days 1-4	Day 7	Weeks 2-4 (weekly)	Week 8	Week 12	Month 6 and every 3 months	At confirmation of PD	LTFU (maximum every 6 months)
Vector Copies (Persistence)	-	-	8	-	8	8	8	8	8	8	8	8	8
VSV-G DNA (RCL)	-	-	8	-	-	-	-	-	-	8	8 [1]	-	8
PBMC (Functional Assays, Immunophenotyping)	-	-	24	-	24	24	24	24	24	24	24	24	-
CK Analysis and HAIC Responses	-	-	3	-	3	3	3	3	3	3	3	3	-
Exosome and cfDNA collection (liquid biopsy)			17										
Total (mL)	-	-	60	-	35	140	35	105	52	35	43 [1]	52	16
Total (tablespoons)	-	-	4.1	-	2.3	9.4	2.3	7.1	3.5	2.3	2.9	3.5	-

1. RCL (8 ml) is only collected at 6 month intervals

7 DEFINITIONS

7.1 Medical History and Physical Examination

The medical history must include all diagnoses and surgical procedures of major organ systems. Any allergies to any medications and their formulations must be documented.

7.2 Previous Medications

All prescription and nonprescription medication, vitamins, herbal and nutritional supplements, taken by the subject during the 30 days prior to screening will be recorded at the screening visit. All anti-cancer treatments must be recorded regardless of time.

7.3 Concomitant Medications

Concomitant medications will be recorded in the medical record and on the appropriate eCRF. In addition, any additions, deletions, or changes of these medications will be documented.

7.4 ECOG Performance Status

Performance status will be assessed by ECOG. If necessary, for reporting purposes, the scale can be converted from Karnofsky using the standard scale shown in **Table 4.**

Table 4: ECOG Performance Status Scale and Karnofsky Index of Performance Status

ECOG (Zubrod) Performance Status Scale		Karnofsky Index of Performance Status	
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.
		90%	Able to carry on normal activity; minor sighs of symptoms of disease.
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.
		70%	Cares for self, unable to carry on normal activity or do active work.
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.
		50%	Requires considerable assistance and frequent medical care.
3		40%	Disabled; requires special care and assistance.

ECOG (Zubrod) Performance Status Scale		Karnofsky Index of Performance Status	
Score	**Description**	**Score**	**Description**
	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	30%	Severely disabled; hospitalization indicated, although death not imminent.
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.
		10%	Moribund, fatal process progressing rapidly.
5	Dead	0%	Patient expired.

7.5 Targeted Physical Examination and Vital Signs

A targeted physical exam will imply assessments in each of the following categories: General (weight, height at screening, blood pressure, pulse, respiration rate, and temperature), head, eyes, ear, nose and throat examinations, lymph node examination, chest and cardiovascular system examination, breasts, respiratory system, abdominal examination, dermatological examination, and neurological examination including mental status assessment.

7.6 Complete Metabolic and Hepatic Panel

Complete metabolic panel will include measurements of sodium, potassium, chloride, bicarbonate, urea nitrogen, uric acid, creatinine, total protein, albumin, calcium, phosphorous, cholesterol, triglycerides, amylase, lipase, and lactic dehydrogenase. Hepatic panel refers to liver function tests will include measurements of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), C-reactive protein (CRP). Prothrombin time (PT) will be listed separately. In the schedule of study procedures, chemistries and liver function tests are always performed together. Additionally, Ferritin will be measured.

7.7 CBC, Differential

Hematology tests will include hemoglobin, hematocrit, platelet count, red cell count, and white cell count with differential count.

7.8 HLA-A*0201, A*0205 and/or A*0206 Screening

A high resolution test for the HLA-A*0201, A*0205 and A*0206 allele is required. At the present time, only HLA-A*0201, HLA-A*0205, and/or HLA-A*0206 subjects are eligible, as the other subtypes (e.g., HLA-A*0202) do not interact with the engineered TCR.

7.9 Dose Limiting Toxicity

A dose limiting toxicity (DLT) is defined as something which is both:

Any untoward or adverse event which seems at least possibly related to the modified TCR therapy

Plus:

Any Grade 3 or higher event that is sustained for more than 1 week, excepting autoimmune disorders and chemotherapy related adverse events. For cytokine release syndrome, the event must be a grade 4 adverse event and sustain at grade 4 for more than 1 week to be considered a DLT.

Any Grade 3 or higher autoimmune disorder that cannot be resolved to less than or equal to a Grade 2 autoimmune toxicity within 100 days should also be deemed a DLT.

Any chemotherapy-related event should not normally be considered a DLT unless the investigator is under the reasonable impression that the modified TCR therapy specifically has made the event worse in which case it will be considered a DLT

8 RESPONSE CRITERIA

8.1 Endpoints and Assessment Methods

Tumor response will be assessed by RECIST 1.1.

Tumor measurements and scan data may be stored at a central imaging vendor as directed by the Sponsor for future central analysis as needed.

8.2 RECIST 1.1 Criteria for Evaluating Response in Solid Tumors

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. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Ultrasound (US) should not be used to measure tumor lesions. The same modality should be used when comparing or making assessments.

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete response.

Cytology and histology can be used in rare cases (e.g., for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease).

Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

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.

8.2.1 Measurable lesions measurement

Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

8.2.2 Measurable lesions

- **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 is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
- **Lytic bone lesions or mixed lytic-blastic lesions** with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
- **'Cystic lesions'** thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

8.2.3 Non-measurable lesions

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

- **Blastic bone lesions** are non-measurable.
- **Lesions with prior local treatment**, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

8.2.4 Target Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
- All measurements should be recorded in metric notation using calipers if clinically assessed. 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, which will be

used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

8.2.5 Non-target Lesions

All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as **non-target lesions** and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

8.2.6 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: the appearance of one or more new lesions is also considered progressions) Note: determination of PD will not be made prior to the Day 60 evaluation.

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.

Special notes on the assessment of target lesions:

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
- Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned. Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of

each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

8.2.7 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 subject to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing 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.

8.2.8 Special notes on assessing progression of Non-Target lesions

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- **When subject has measurable disease**. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- **When subject has only non-measurable disease.** There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

8.2.9 New lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something

other than tumor, especially when the subject's baseline lesions show partial or complete response).

- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up - is PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Table 5: Summary of the overall response status calculation at each time point:

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required**[1]
CR	CR	No	CR	≥4 wks. Confirmation[2]
CR	Non-CR Non-PD	No	PR	≥4 wks. Confirmation[2]
CR	Not evaluated	No	PR	
PR	Non-CR Non-PD Not evaluated	No	PR	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[1]
SD	Non-CR Non-PD Not evaluated	No	SD	Documented at least once ≥4 wks. from baseline[2]
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD[3]	Yes or No	PD	
Any	Any	Yes	PD	

(1) See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

(2) Only for non-randomized trials with response as primary endpoint

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

8.2.10 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

8.2.11 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf

9 STATISTICAL ASSESSMENT

9.1 Study Populations

Intent-to-Treat (ITT) population: all subjects who were enrolled in the trial. The ITT population is the primary population for the safety of the end-to-end autologous T cell therapy procedure.

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

9.2 Statistical methods for demographics and safety parameters

With respect to the primary objectives and endpoints, no specific statistical hypotheses are being evaluated. The primary focus will be on determining the safety profile, and the pharmacodynamics of NY-ESO-1^{c259}T cells following infusion. All analyses will be descriptive and exploratory and may be performed by cohorts and / overall cohorts.

Descriptive statistics will be provided for selected demographic, safety, imaging, and cytokine assessments as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges. Categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

9.3 Statistical analysis and reporting methods for safety endpoints

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

9.3.1 Adverse Events

All adverse events will be listed and coded by MedRA. The number and percent of patients reporting any 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 classified by severity, relationship to treatment and seriousness in tabulation. 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.

9.3.2 Vital Signs

Vital signs will be listed and summarized

9.3.3 Electrocardiogram

Electrocardiogram data will be listed for each patient. Fridericia's and/or Bazett's correction will be used to adjust QT for RR. Further details on reporting of EKG data can be will be provided in the RAP.

9.3.4 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.

9.3.5 T cell Phenotype and Cytokines

The results will be listed.

9.3.6 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. 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.

9.4 Statistical analysis and reporting methods for efficacy endpoints

To determine the effect of the treatment of NY-ESO-1^{C259}T cell infusion on tumor response, summaries of efficacy will be based on overall response rate (ORR); best overall response (BOR); time to and duration of response; progression free survival (PFS); and the overall survival (OS) by cohort.

Primary Analyses –Primary analyses will be based on RECIST 1.1 measurement ORR is defined as the percentage of subjects with a confirmed CR or PR 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 percentage). Appropriate methods for calculated CIs will be utilized, these will be identified in the analysis plan. Tumor measurements and scan data may be stored at a central imaging vendor as directed by the Sponsor for future central analysis as needed.

Further details about the efficacy analyses will be outlined in the RAP.

The duration of response will be summarized descriptively for subjects using Kaplan-Meier medians. Duration of response is defined, for the subset of subjects with a confirmed CR or PR, as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause.

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 using 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.

Further details on rules for censoring and about the efficacy analyses will be provided in the RAP.

10 CORRELATIVE DATA ANALYSIS

10.1 General Overview

In this section, a comprehensive summary of potential correlative studies is provided. This description is based on the current data available to the investigators. Some studies may not be performed, or different studies may be performed, based on the data emerging from the study, availability of samples, or other factors.

10.2 Core Correlative Studies

For molecular (Q-PCR and Q-RT-PCR), immune phenotyping and functional assays, peripheral blood will be collected. For cytokine analyses peripheral blood samples will be collected in serum separator (SST) tubes. Samples will be collected according to the sample collection schedule (Table 2).

Samples will be shipped to a Central Lab. All research analyses will be performed based on principles of good laboratory practice, with assay-specific SOP using qualified and if possible validated assays. Documentation for sample receipt, processing and storage, and primary data from the research analyses will be collected and stored at the Central Lab.

If a subject has an adverse event, an additional biopsy (for example skin, GI tract, bone marrow, tumor) or blood (serum and PBMC) samples may be requested with the objective of gaining an understanding of the underlying etiology of the adverse event. The below described research tests may be performed on these samples.

10.2.1 Evaluation of Tumor

Analysis of tumor biopsies for the purpose of study enrollment is detailed in Section 3.3.3. In patients where follow up tumor biopsies are safely accessible, additional tumor biopsies will be analyzed for tumor expression of the tumor antigen target; HLA expression, and infiltration by lymphocytes. These analyses will be performed either by the Central Lab or other laboratory as indicated by the Sponsor.

10.2.2 T Cell Function and Phenotype

Measurement of the following immunological parameters associated with product bioactivity and functionality is planned and will be performed at the Central Lab or by the laboratories at the sites.

- **Persistence of Infused Cells in the Periphery:** Persistence and homing of infused gene marked cells to tumor will be evaluated using a qualified Q-PCR assay and DNA isolated directly from peripheral blood samples, by quantifying. If persistence levels are high enough (> 0.1% of total DNA), flow cytometric analysis using multimer-reagents for the NY-ESO-1 TcR will be used as an independent, secondary measure of persistence
- Selective migration and engraftment of gene-modified infused cells to the tumor.
- The ex-vivo immune functionality and phenotype of infused and persisting cell: will be evaluated directly ex-vivo and will be possible if persistence levels are shown to be greater than 0.5% of total

cells. Functionality will be evaluated by measuring antigen-specific degranulation and intracellular cytokine production in response to target cells that express the HLA-A02 gene as well as NY-ES0-1 and. Surface differentiation and memory phenotype will be determined using multi-parameter flow cytometry and co-staining for markers such as CD45RO, CCR7, CD27, CD28, and CD57. If sufficient material is available, parallel analyses may evaluate expression of exhaustion and activation markers: PD1, CD154, CD95, CD25, and CD127.

- The modulation of cytokine milieu in periphery: luminex will be used to evaluate cytokine levels such as: IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40⁄p70), IL-13, IL-15, IL-17, TNF-α, IFN-α, IFN-γ, GM-CSF, MIP-1α, MIP-1β, IP-10, MIG, Eotaxin, RANTES, MCP-1, VEGF, G-CSF, EGF, FGF-basic, and HGF. IL-6, TNF-α, IFN-γ will be evaluated at a minimum.
- Evaluation of the immune milieu in tumor biopsies will be possible if sufficient tumor material is obtained during the post-treatment biopsies. These analyses will be performed by Q-RT-PCR and will measure the influx of immune cell subsets such as CD3, CD4, CD8, CD14, CD16, CD19, CD206, T cell activation such as CD25, CD95, CD154, T cell exhaustion (PD1, CD57), as well as inflammatory cytokines such as IFN-γ, TNF-α, IL-8, IL-10, and IL-2.
- The development of an expanded patient immune response against tumor via epitope spreading. Each of these analyses will be performed in bulk on samples procured according to the schedule in Table 2, processed and frozen as per SOP.

10.2.3 Exploratory Dose- and Exposure-Response Analysis

The relationship between number/composition of infused cells (dose) and/or persistence of infused cells in the periphery (exposure) and changes in immune cell phenotype, cytokine production and tumor size will be assessed as data permit. Relationship between dose/exposure and measures of response (immune cell phenotype/cytokines/tumor size) will be initially assessed via graphical methods. If data warrant, further analysis of dose- and/or exposure-response via population non-linear mixed effects modeling may be performed.

10.2.4 Evaluation of Epitope Spreading

In order to determine the development of an expanded patient immune response against tumor via epitope spreading, cellular immunity may be analyzed. NY-ESO-1 specific $CD4^+$ and $CD8^+$ T cell reactivity may be measured by:

- Cytokine secretion (Gnjatic, Nagata et al. 2000; Gnjatic, Atanackovic et al. 2003; Odunsi, Qian et al. 2007).
- Enzyme Linked Immunospot (ELISPOT) (Gnjatic, Nagata et al. 2000; Gnjatic, Atanackovic et al. 2003; Odunsi, Qian et al. 2007).
- MHC multimer (Gnjatic, Nagata et al. 2000; Gnjatic, Atanackovic et al. 2003; Odunsi, Qian et al. 2007)

For ELISPOT assays, a response will be considered positive if the number of spots in the peptide-exposed well is two-fold or more higher than the number of spots in the unstimulated well, and if there is a minimum of ten (after subtraction of background spots) peptide-specific spots/25,000 T cells. The FACS analysis following in-vitro-presensitization will serve as the primary assay for the determination if a patient is considered an immune responder. For FACS analysis, immune response is defined as positive if the frequency of T cells detected in at least one post-vaccine sample exceeds by ≥ 3-fold that found in the baseline sample.

10.2.5 Liquid biopsy collection and analysis

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

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

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

10.2.6 Ascites fluid collection and analysis

Ascites samples have been shown to be a rich source of tumor cells, tumor infiltrating leukocytes and soluble factors, changes in which have been reported to correlate with disease prognosis and response to therapy. Ascites fluid collected in this protocol will be used to interrogate soluble and cellular components of the tumor microenvironment before and after T cell infusion to address mechanisms of sensitivity or resistance to therapy.

Research studies conducted in ascites samples may include cellular and molecular assays (on DNA and RNA) aiming at:

- Analyzing antigen expression by tumor cells,
- Analyzing persistence and phenotype of genetically modified T cells by qPCR and flow cytometry,
- Assessing T cell-receptor diversity and clonality,
- Evaluating candidate biomarkers of immune response, anti-tumor activity and resistance to therapy, through gene expression analysis (by RNA-Seq, Nanostring or RT-PCR).

As new technologies and data emerge, other assays relevant to the study objectives may be performed.

10.2.7 Request for Autopsy for Death Following Administration of Gene Transfer Agents

In accordance with FDA and EMA guidance [FDA, 2006b; EMA 2009], all subjects enrolled in this trial are asked to consider an autopsy and autopsies will be requested of the families for all subjects who die during participation in studies after administration of gene transfer agents. To ensure compliance, guidelines for performing an autopsy are provided in the Study Procedures Manual.

10.2.8 Additional Exploration of the T Cell Response

The methods to analyze the T cell response to cancer antigens used in this study are well established. However, as T cell biology and immune regulation are very active fields of discovery, the opportunity exists to refine and extend the analysis of the T cell response. This work may also involve establishing cell lines and clones in culture, and collaborations with investigators.

11 SAFETY AND ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal.
- is associated with a serious adverse event.
- is associated with clinical signs or symptoms.
- leads to additional treatment or to further diagnostic tests.
- is considered by the investigator to be of clinical significance.

11.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

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-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

11.1.3 Intensity

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 as follows:

NCI 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 patient 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.

11.1.4 Assessment of Causality

An investigator who is a qualified physician will assess the causal relationship between the adverse event and NY-ESO-1^{c259}T according to his/her best clinical judgement. The following scale of criteria will be used as a guidance.

Causality Term	Assessment Criteria
Not related	• The patient did not receive the test drug. Or • Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. Or • There is another obvious cause of the AE.
Possibly related	• There is evidence of exposure to the test drug. • The temporal sequence of the AE onset relative to administration of the test drug is reasonable • The AE could have been due to another equally likely cause.
Probably related	• There is evidence of exposure to the test drug. • The temporal sequence of the AE onset relative to administration of the test drug is reasonable. • The AE shows a pattern consistent with previous knowledge of the test drug or test drug class • The AE is more likely explained by the test drug than by any other cause.
Definitely related	• There is evidence of exposure to the test drug. • The temporal sequence of the AE onset relative to administration of the test drug is reasonable. • The AE shows a pattern consistent with previous knowledge of the test drug or test drug class. • The AE is most likely explained by the test drug, any other cause is improbable.

11.1.5 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, a reasonable possibility is at least “possibly related" according to the table above.

11.1.6 Unexpected Suspected Adverse Reaction (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.7 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

11.1.8 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

11.1.9 Post-Study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, stabilized, or the adverse event is otherwise explained with the subject under the care of a qualified medical practitioner. At the last scheduled visit, the investigator should instruct each subject to report any subsequent serious adverse event(s) that the subject, or the subject’s personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

11.1.10 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- Is associated with clinical signs or symptoms or suggests a disease and/or toxicity
- Requires treatment or any other therapeutic intervention
- Results in study treatment dose modification, interruption or discontinuation from the study.
- Is associated with death or another serious adverse event, including hospitalization. Is judged by the Investigator to be of significant clinical impact
- Any CTCAE lab value≥ Grade 3 should be recorded as an AE. Any value < Grade 3 may still be an AE if judged clinically significant.
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

11.1.11 Progression of underlying malignancy

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

11.1.12 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

11.2 Recording of Adverse Events

Adverse events will be assessed using CTC V4. At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF/eCRF). All signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events, whether considered related to the study drug or not, occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up 30 days after the end of the study or, if related to treatment, until resolution or stabilization to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

11.2.1 Adverse Event Reporting Period

Patients will be monitored for the duration of the intervention protocol, not including long term follow-up for AE reporting. The AE reporting period begins at apheresis until completion.

During long term follow-up (years 1 - 15), patients will only be monitored for delayed adverse events related to the gene transfer aspect of the protocol. These are defined in Section 5.12.

11.3 Reporting of Serious Adverse Events and Unanticipated Problems

11.3.1 Reporting Criteria during the Study Intervention Period (Apheresis up to discontinuation)

- All adverse events should be reported, not just those considered related.

If an event meets the criteria definition of a serious adverse event, the investigator or designee (initial reporter) must complete a Serious Adverse Event Report (provided as an attachment on the study Manual of Operating Procedures -MOP) with at least minimum information as available for the event. Minimum reporting criteria include:

Identifiable patient

Suspect medicinal product

Identifiable reporting source (with signatures)

Event that is identified as serious

Severity and grading of event

Relationship to suspect medication.

The initial reporter or designee (Site Coordinator / Investigator) must e-mail the completed SAE Report Form with all available information **as soon as possible and always within 24 hours** of learning of the SAE to: **ADPSafety@SCiAN.com.**

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

Due to the nature of the treatment, patients are required to be followed for up to 15 years after treatment with genetically modified T cells. Patients will be followed according the schedule outlined in Section 5.12. 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 hematologic disorder
- Gene marking of the surrogate sample

Only adverse events deemed related to the gene modified cells are captured by Adaptimmune and reported to the regulatory agencies. The detailed description of the event should include the date of diagnosis and the nature of the diagnosis. If the diagnosis is cancer, record the type and stage of the cancer. If the cancer is metastatic, list the metastatic sites.

If a new malignancy is recorded in a vector target cell type, tumor cells will be evaluated for vector sequences.

11.4 Investigator Reporting of SAEs: Notifying the Study Sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the study sponsor within 24 hours of the Investigator/site staff learning of the SAE.

For specific instructions for reporting SAEs to the Sponsor, please see the Manual of Procedures for the study, or contact the study manager at Adaptimmune.

The investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor. SAEs should be followed until resolution.

11.5 Investigator Reporting to the IRB

Investigators at each site are responsible for safety reporting to their IRB. Investigators are responsible for complying with their IRB's reporting requirements.

11.6 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global law and regulations.

11.7 Stopping Rules

If the following events occur, further enrolment to the study may be suspended on the basis of a joint review of the information/data by the Sponsor and Investigators, and pending approval of a subsequent protocol amendment (if appropriate):

Any death occurs that is deemed to be probably or definitely related to the investigational medication/cell product;

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 RCL occurs and no additional lot of vector is available (see Section 11.10.1 on Monitoring for and Management of replication competent Lentivirus (RCL)).

11.8 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

11.9 Data Monitoring Committee

The data for this study will be closely monitored by the Sponsor. There is no formal Data Monitoring Committee for this study.

11.10 Safety Monitoring

11.10.1 Monitoring and Management of Replication-Competent Lentivirus (RCL)

Replication Competent Lentivirus (RCL) is a theoretical risk associated with the use of lentiviral vectors; no RCL has ever been detected in vitro or in vivo. The risk is derived from the detection of replication competent retrovirus (RCR) during the use of early γ retroviral vector packaging systems which were inadequately designed to avoid recombination events between the vector and packaging components [Miller, 1990]. Updated γ retroviral packaging systems have not been associated with RCR. However in a study with Rhesus monkeys, three out of 10 animal died of lymphomas at around 6 months after transplantation of vector transduced bone marrow cells contaminated with replication-competent virus [Donahue, 1992]. Therefore, RCR/L must continue to be rigorously evaluated in vector and cell lots, and

in subjects post infusion with any product involving a retrovirus [FDA, 2006a; FDA, 2006b; FDA, 2010; FDA, 2009].

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

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

The following approaches have been discussed for subject management:

Provide targeted antiretroviral therapies based on genotyping of the RCL.

Intensive follow up of subject in consultation with gene therapy experts, study investigators, HIV physicians, FDA and NIH.

11.10.2 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:

1. The cell product, whereby RCL testing will be performed by or under the direction of the manufacturing facility responsible for manufacturing and release of the vector.
2. Patient's PBMCs will be collected prior to infusion of transduced T cells and then at 3, 6, and 12 months post treatment. If these tests are negative at all time points during the first year, PBMC samples will be collected annually and archived for up to 15 years post infusion or until assessments for persistence have ended (Section 11.10.4.1); however, if VSV-G DNA copies are detected at any time point in the first year post-infusion, the safety monitoring protocol (Section 11.10.311.10.3) will be triggered. Subject samples will continue to be tested for VSV-G DNA copies until VSV-G DNA copies are not detected for 3 consecutive annual assessments, then

subject samples will be collected annually until year 15 and archived at Adaptimmune's centralized biomarker repository or until assessments for persistence have ended (Section 11.10.4.1).

11.10.3 Safety Monitoring Results

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

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 will be performed on the leukapheresis product. The biological RCL test assesses whether there is active production of infectious viral particles from the leukapheresis product [Manilla, 2005].

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

11.10.4 Persistence Testing and Monitoring for Insertional Oncogenesis

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

11.10.4.1 Testing for Persistence of Gene Marked Cells in Clinical Studies

Peripheral blood mononuclear cell (PBMCs) samples will be collected and used as the "surrogate sample" for monitoring persistence of gene modified cells in subjects prior to infusion of transduced T cells and at 3, 6 and 12 months post-infusion, then every 6 months until 5 years post-infusion and every year from year 6 post infusion in accordance with the FDA and EMA guidance [FDA, 2006a; FDA, 2006b; EMA, 2009]. The samples will be tested using a PCR-based method to detect the presence of the Psi gene, which is part of the lentiviral vector used to transduce T cells. Detection of Psi DNA copies reflects persistence of the genetically modified T cells. If at 1 year or beyond post-infusion greater than 1% PBMCs test positive for the vector sequence, the subject's PBMCs will be evaluated for integration site analysis (see Section 11.10.4.2). If no gene modified cells are detected for three consecutive assessments post-infusion, and the subject is more than 5 years post-infusion, no further monitoring of PBMCs is required

and collection of samples for persistence may be stopped. All other assessments such as RCL, hematology and chemistry may also be stopped. The subject will continue to be followed by the Investigator, local oncologist or local physician by phone call or survey for up to 15 years post-infusion.

11.10.4.2 Testing for Insertional Oncogenesis

If persistence, as detected by the presence of a vector sequence (Psi DNA copies), is present in >1% of PBMC at 1 year or beyond post-infusion, DNA from the subject's PBMCs will be sent for integration site analysis. Integration site analysis will also assess the possibility of insertional oncogenesis.

If there is clonal dominance in the genetically modified T cell population (either monoclonality or oligoclonality) the persistence assessment will be repeated within 3 months on a new sample. If the repeated analysis demonstrates: 1) persistent monoclonality, 2) evidence of insertional oncogenesis or 3) clonal expansion, there will be a review by Adaptimmune's Safety Review Team and Safety Governance Board to develop a monitoring plan specific to the health care risk, and/or strategies to inform appropriate subjects, investigators, and regulators of the findings. If the integration site analysis indicates polyclonality of the genetically modified T cell population, then screening will continue as scheduled.

12 Administration

12.1 Data Handling and Record Keeping

12.1.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

It is the responsibility of the investigator and the study staff to maintain a comprehensive and centralized filing system of all relevant study documentation. Such documentation includes:

1. eCRFs: must be kept accurate and up-to-date.
2. Subject Files/Signed Informed Consent: which substantiates the data entered in the EDC system for all required test and evaluation procedures and verifies that the subject has signed an informed consent to enter the study prior to any study-related procedures being performed.
3. Subject Exclusion Record: which should reflect the reason any subject was screened and found ineligible for the study.
4. Monitoring Log: listing dates of monitor visits.
5. Regulatory Documents: including, but not limited to, protocol and signature form, IB, FDA Form 1572, Financial DisclosureForm, laboratory certification and accreditations, laboratory normal ranges, CVs, IRB/IEC correspondence, IRB/IEC approval/renewals, IRB/IEC approved consent form, etc.
6. SAE Report Forms: which should document any SAEs.

12.1.2 Case Report Forms

The study case report form (CRF/eCRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded within the timeframe established by contract of subjects' visit. In case of an SAE, the data must be recorded immediately. All missing data must be explained.

12.1.3 Records Retention

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

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

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

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

12.2 Departure from the Protocol

There should be no departure from the protocol if at all possible. If an emergency occurs that requires departure from this protocol, the investigator will, if circumstances and time permit, contact the Sponsor. Such contacts will be made to permit a decision as to whether or not the subject will continue in the study. Such departures need to be clearly documented and reported to the IRB/IEC by the investigator.

12.3 Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Confidentiality of Data

Data generated by this study will be considered confidential by the investigator under the terms expressed in the clinical trials agreement between the Sponsor and each Investigator.

13.2 Confidentiality of Subject/Patient Records

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to SPONSOR.

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance will all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

13.3 Compliance with law, audit, and debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practices; and all applicable federal, state and local laws, rules and regulations relating the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee Review, and regulatory agencies inspection of trial related documents and procedures and provide for direct access all study-related source data and documents.

The investigator agrees not to intentionally seek reimbursement from subjects/patients, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the SPONSOR.

The investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations. Following reasonable notice by Sponsor, study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request for each subject/patient participating in the study, and upon completion or termination of the clinical study and as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR, or requirements from regulatory agencies. In addition, this information shall be made available at the investigator's site upon request and for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory

agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPOSNOR as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct work on this SPONSOR's study. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the SPONSOR prematurely terminates a particular study site, the SPONSOR will promptly notify the site's IRB/IEC.

13.4 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.

13.5 Subject Stipends or Payments

Stipends or payments to subjects are as dictated by the site level contracts and IRB/EC approved consent forms.

13.6 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent

form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

13.7 Public Posting of Study Information

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

13.8 Clinical Study Report

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

13.9 Publication Policy

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

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

14 APPENDICES

Appendix A: Sample Patient Letter for Long Term Follow-Up

[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 ovarian cancer).
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 (e.g., 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 Phase I/IIa, Open Label, Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer"

". 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.

[study coordinator]

Appendix B : 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**:

1. New malignancies
2. New incidence of exacerbation of a pre-existing neurologic disorder
3. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
4. New incidence of a hematologic disorder.

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 #(XXXXXX), patient ID (XXX) and the study title which is "A Phase I/IIa, Open Label, Clinical Trial Evaluating the Safety and Efficacy of Autologous T Cells Expressing Enhanced TCRs Specific for NY-ESO-1 in Patients with Recurrent or Treatment Refractory Ovarian Cancer

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]

Appendix C: Long Term Follow Up

Long Term Follow Up – Years 1-5		
Assessment	*Every 6 months*	*Annually*
Physical Exam	X	
Medical History	X	
Concomitant Meds	X	
AE Collection *(only delayed AEs related to gene transfer are captured)*	X	
Chemistries	X	
CBC	X	
Cell collection for RCL archive		X
Persistence of Vector Sequences	X	
Long Term Follow Up – Years 6-15		
Assessment	*Annual office visits if vector modified cells were detected in the previous visit. If yes, RCL testing (archive) is collected*	*If vector modified cells were not detected, follow up can be conducted by means of clinical questionnaire thorough an annual phone call or postcard*
Physical Exam	X	
Medical History	X	
Concomitant Meds	X	
AE Collection *(only delayed AEs related to gene transfer are captured)*	X	X
Chemistries	X	
CBC	X	
Persistence of Vector Sequences	X	
Interview		X

Appendix D: Tocilizumab Drug Information

Initial U.S. Approval: 2013

U.S. BRAND NAMES: ACTEMRA® (tocilizumab)

ADMINISTRATION: Injection, for intravenous infusion

ADVERSE REACTIONS: Most common adverse reactions (incidence ≥ 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT.

WARNINGS AND PRECAUTIONS

Serious Infections
Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA for rheumatoid arthritis. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

ACTEMRA should not be administered in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.

ACTEMRA should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Tuberculosis
Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ACTEMRA. Anti-tuberculosis therapy should also be considered prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy. It is recommended that patients be screened for latent tuberculosis infection prior to starting ACTEMRA. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA.

Viral Reactivation
Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

Gastrointestinal Perforations
Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis. ACTEMRA should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Laboratory Parameters

Neutrophils
Treatment with ACTEMRA was associated with a higher incidence of neutropenia. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience. It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count i.e., absolute neutrophil count (ANC) <2000/mm3. In patients who develop an absolute neutrophil count <500/mm3 treatment is not recommended. Neutrophils should be monitored every 4 to 8 weeks.

Platelets
Treatment with ACTEMRA was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials. It is not recommended to initiate ACTEMRA treatment in patients with a platelet count below 100,000/mm3. In patients who develop a platelet count <50,000/mm3 treatment is not recommended. Platelets should be monitored every 4 to 8 weeks.

Liver Function Tests
Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA. In one case, a patient who had received ACTEMRA 8 mg/kg monotherapy without elevations in transaminases experienced elevation in AST to above 10x ULN and elevation in ALT to above 16x ULN when MTX was initiated in combination with ACTEMRA. Transaminases normalized when both treatments were held, but elevations recurred when MTX and ACTEMRA were restarted at lower doses. Elevations resolved when MTX and ACTEMRA were discontinued. It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST > 1.5x ULN. In patients who develop elevated ALT or AST > 5x ULN treatment is not recommended. ALT and AST levels should be monitored every 4 to 8 weeks. When clinically indicated, other liver function tests such as bilirubin should be considered.

Lipids
Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol. Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 6 month intervals. Patients should be managed according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Immunosuppression
The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with infusion of ACTEMRA. Appropriate medical treatment should be available for immediate use in the event of an anaphylactic reaction during administration of ACTEMRA.

Demyelinating Disorders
The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

Active Hepatic Disease and Hepatic Impairment
Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment.

Vaccinations
Live vaccines should not be given concurrently with ACTEMRA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA. No data are available on the effectiveness of vaccination in patients receiving ACTEMRA. Because IL-6 inhibition may interfere with the normal immune response to new antigens, patients should be brought up to date on all recommended vaccinations, except for live vaccines, prior to initiation of therapy with ACTEMRA.

MECHANISM OF ACTION -- Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signalling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

Appendix E: Cyclophosphamide: Drug Information

U.S. BRAND NAMES — Cytoxan®

PHARMACOLOGIC CATEGORY
Antineoplastic Agent, Alkylating Agent

ADMINISTRATION: I.V. infusions may be administered over 1-24 hours.
Doses >500 mg to approximately 2 g may be administered over 20-30 minutes.
To minimize bladder toxicity, increase normal fluid intake during and for 1-2 days after cyclophosphamide dose. Most adult patients will require a fluid intake of at least 2 L/day. High-dose regimens should be accompanied by vigorous hydration with or without mesna therapy.

ADVERSE REACTIONS SIGNIFICANT
Greater than 10%:
Dermatologic: Alopecia (40% to 60%) but hair will usually regrow although it may be a different color and/or texture. Hair loss usually begins 3-6 weeks after the start of therapy.
Endocrine & metabolic: Fertility: May cause sterility; interferes with oogenesis and spermatogenesis; may be irreversible in some patients; gonadal suppression (amenorrhea)
Gastrointestinal: Nausea and vomiting occur more frequently with larger doses, usually beginning 6-10 hours after administration; anorexia, diarrhea, mucositis, and stomatitis are also seen
Genitourinary: Severe, potentially fatal acute hemorrhagic cystitis, believed to be a result of chemical irritation of the bladder by acrolein, a cyclophosphamide metabolite, occurs in 7% to 12% of patients and has been reported in up to 40% of patients in some series. Patients should be encouraged to drink plenty of fluids during therapy (most adults will require at least 2 L/day), void frequently, and avoid taking the drug at night. With large I.V. doses, I.V. hydration is usually recommended. The use of mesna and/or continuous bladder irrigation is rarely needed for doses <2 g/m2.
Hematologic: Thrombocytopenia and anemia are less common than leukopenia. Onset: 7 days, Nadir: 10-14 days, Recovery: 21 days
From 1% to 10%:
Cardiovascular: Facial flushing
Central nervous system: Headache
Dermatologic: Skin rash
Renal: SIADH may occur, usually with doses >50 mg/kg (or 1 g/m2); renal tubular necrosis, which usually resolves with discontinuation of the drug, is also reported
Respiratory: Nasal congestion occurs when I.V. doses are administered too rapidly (large doses via 30-60 minute infusion); patients experience runny eyes, rhinorrhea, sinus congestion, and sneezing during or immediately after the infusion. If needed, a decongestant or decongestant/antihistamine (eg, pseudoephedrine or pseudoephedrine/triprolidine) can be used to prevent or relieve these symptoms.

Less than 1% (Limited to important or life-threatening): High-dose therapy may cause cardiac dysfunction manifested as CHF; cardiac necrosis or hemorrhagic myocarditis has occurred rarely, but may be fatal. Cyclophosphamide may also potentiate the cardiac toxicity of anthracyclines. Other adverse reactions include anaphylactic reactions, darkening of skin/fingernails, dizziness, hemorrhagic colitis, hemorrhagic ureteritis, hepatotoxicity, hyperuricemia, hypokalemia, jaundice, neutrophilic eccrine hidradenitis, radiation recall, renal tubular necrosis, secondary malignancy (eg, bladder carcinoma), Stevens-Johnson syndrome, toxic epidermal necrolysis; interstitial pneumonitis and pulmonary fibrosis are occasionally seen with high doses

BMT:
Cardiovascular: Heart failure, cardiac necrosis, pericardial tamponade
Endocrine & metabolic: Hyponatremia
Hematologic: Methemoglobinemia
Gastrointestinal: Severe nausea and vomiting
Miscellaneous: Hemorrhagic cystitis, secondary malignancy

MECHANISM OF ACTION — Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

Appendix F: Mesna: Drug Information

U.S. BRAND NAMES — Mesnex®

PHARMACOLOGIC CATEGORY
Antidote; Uroprotectant

ADMINISTRATION: For IV administration, the required dose of mesna should be withdrawn from the multidose vial labeled as containing 100 mg/mL and diluted with an appropriate volume of a compatible IV solution (i.e., 5% dextrose; 5% dextrose and 0.2, 0.33, or 0.45% sodium chloride; 0.9% sodium chloride; lactated Ringer's) to obtain a solution containing 20 mg/mL. The diluted solution may then be given by direct IV injection or infused IV over a period of 15–30 minutes.

ADVERSE REACTIONS SIGNIFICANT
Mesna monotherapy: Headache, injection site reactions, flushing, dizziness, nausea, vomiting, somnolence, diarrhea, anorexia, fever, pharyngitis, hyperesthesia, influenza-like symptoms, coughing, constipation, flatulence, rhinitis, rigors, back pain, rash, conjunctivitis, arthralgia.

Mesna alone (frequency not defined):
Cardiovascular: Flushing
Central nervous system: Dizziness, fever, headache, hyperesthesia, somnolence
Dermatologic: Rash
Gastrointestinal: Anorexia, constipation, diarrhea, flatulence, nausea, taste alteration/bad taste (with oral administration), vomiting
Local: Injection site reactions
Neuromuscular: Arthralgia, back pain, rigors
Ocular: Conjunctivitis
Respiratory: Cough, pharyngitis, rhinitis
Miscellaneous: Flu-like syndrome

Mesna alone or in combination: Post-marketing and/or case reports: Allergic reaction, anaphylactic reaction, hypersensitivity, hyper-/hypotension, injection site erythema, injection site pain, limb pain, malaise, myalgia, platelets decreased, ST-segment increased, tachycardia, tachypnea, transaminases increased

MECHANISM OF ACTION — In blood, mesna is oxidized to dimesna which in turn is reduced in the kidney back to mesna, supplying a free thiol group which binds to and inactivates acrolein, the urotoxic metabolite of ifosfamide and cyclophosphamide

Appendix G: Fludarabine: Drug Information

U.S. BRAND NAMES — Fludara®

Availability: Fludarabine monophosphate is commercially available and will be supplied by the pharmacy of the enrolling institution. FLUDARA IV, is supplied as a white, lyophilized powder. Each vial contains 50 mg of fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust pH. Fludara is stored at room temperature.

Storage and Stability: Reconstituted FLUDARA IV is chemically and physically stable for 24 hours at room temperature, or for 48 hours if refrigerated. Because reconstituted FLUDARA IV contains no antimicrobial preservative, care must be taken to assure the sterility of the prepared solution; for this reason, reconstituted FLUDARA IV should be used or discarded within 8 hours.

Preparation: FLUDARA IV should be prepared for parenteral use by aseptically adding Sterile Water for Injection, USP. When reconstituted with 2 ml of Sterile Water for Injection, each ml of the resulting solution will contain 25 mg of Fludarabine Phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7-8.5. The product may be further diluted for intravenous administration in 50 ml of 5% Dextrose for Injection USP, or in 0.9% Sodium Chloride, USP.

Administration: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Fludarabine will be mixed in 50 ml of 0.9% NaCl, and infused i.v. over 30 minutes.

Toxicity: Fludarabine toxicities include myelosuppression (dose limiting toxicity), fever, nausea, vomiting, stomatitis, diarrhea, gastrointestinal bleeding, anorexia, edema, skin rashes, myalgias, headache, agitation, hearing loss, transient episodes of somnolence and fatigue, autoimmune hemolytic anemia, autoimmune thrombocytopenia, paresthesias, peripheral neuropathy, renal, and pulmonary toxicity (interstitial pneumonitis). Severe fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status has occurred after very high doses (approximately 4 times higher than the standard doses employed in this protocol). Severe neurologic toxicity has only rarely been demonstrated at the 25-30 mg/m^2/day dosage of fludarabine. Rarely describe complications include transfusion-associated graft-versus-host disease, thrombotic thrombocytopenic purpura, and liver failure. Tumor lysis syndrome following fludarabine administration has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed post-fludarabine, especially in heavily pre-treated individuals, and in individuals receiving fludarabine combined with other agents.

Note: Investigators should refer to manufacturer prescribing information on each drug for full details on safety and administration.

Appendix H: Summary of Changes from Protocol Version 6 to Version 7

Section of Protocol Version 6	Section of Protocol Version 7	Change
Table of Contents	Table of Contents	Updated for current version
NA	1.1.5	New section added: Rationale for NY-ESO-1 Threshold
1.2; 4.1; 5.3	1.2; 4.1; 5.3	Text edited to more accurately reflect process
1.5	1.5	Editorial change
1.4.2; 3.3.1	1.4.2; 3.3.1	Study progress updated to reflect current status
3.1	3.1	Inclusion criteria for antigen expression edited to change the threshold and reflect standard protocol template language as determination of positive expression managed by central laboratory
3.3.4	3.3.4	Text edited to reflect current inclusion wording
4.5.2	4.5.2	Additional storage detail added
5.12	5.12	Text edited to more accurately reflect process
15	15	Missing references added

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