Cover Page

Official Study Title	TUMOR-ASSOCIATED ANTIGEN (TAA)-SPECIFIC CYTOTOXIC T LYMPHOCYTES ADMINISTERED IN PATIENTS WITH PANCREATIC CANCER (TACTOPS)
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TUMOR-ASSOCIATED **A**NTIGEN (TAA)-SPECIFIC **C**YTOTOXIC **T** LYMPHOCYTES ADMINISTERED **I**N PATIENTS WITH PANCREATIC **C**ANCER (TACTOPS)

PRINCIPAL INVESTIGATORS

Ann M. Leen, PhD
Benjamin Musher, MD

CO-INVESTIGATORS
Helen Heslop, MD
Adrian Gee, PhD
Bambi Grilley, RPh
Carlos Ramos, MD
Premal Lulla, MD
George Carrum, MD
Tannaz Armaghany, MD

STATISTICAL CO-INVESTIGATOR
Tao Wang, PhD

Center for Cell and Gene Therapy

Houston Methodist Hospital
6565 Fannin St.
Houston, TX 77030-2707

Dan L. Duncan Comprehensive Cancer Center
Baylor College of Medicine

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1.0 CHECKLIST FOR PATIENT ELIGIBILITY AND NECESSARY INFORMATION

TUMOR CTL PROTOCOL (PROCUREMENT)

PATIENT ID_____**PATIENT NAME**_____

YES	NO	
Any "**NO**" answers will make a patient **ineligible** for study participation.		
		Any patient with biopsy proven pancreatic adenocarcinoma
		Life expectancy of ≥ 6 months
		Age ≥ 18
		Hgb ≥ 7.0 g/dl (transfusion allowed)
		Informed Consent explained to, understood by and signed by patient. Patient given copy of informed consent.

YES	**NO**	
Any "**YES**" answers will make a patient **ineligible** for study participation.		
		Severe intercurrent infection
		Active infection with HIV (can be pending at this time)

Signature of MD_____**Date**_____

To check eligibility of a patient, telephone Dr. Musher at 713-798-3750. To register a patient, telephone Catherine Robertson (research coordinator) at the Center for Cell and Gene Therapy (832-824-4594).

PATIENT ID_____**PATIENT NAME**_____

TUMOR CTL PROTOCOL (TREATMENT)

YES NO VALUE/DATE

Any **"NO"** answers will make a patient **ineligible** for study participation:

YES	NO	VALUE/DATE	
Any "**NO**" answers will make a patient **ineligible** for study participation.			
			Any patient with biopsy proven pancreatic adenocarcinoma who has: **Group A:** Patients with locally advanced or metastatic pancreatic adenocarcinoma who experienced a documented best response of investigator assessed confirmed PR or SD per RECIST v1.1 **Group B**: Patients with locally advanced or metastatic pancreatic adenocarcinoma who experienced progressive disease following first line chemotherapy or who are judged by the investigator as being ineligible to receive standard of care chemotherapy **Group C**: Patients with potentially resectable pancreatic cancer, who have completed planned preoperative neo-adjuvant chemotherapy, radiotherapy or combination chemoradiation
			Life expectancy of ≥ 12 weeks.
			Measurable or evaluable disease per RECIST 1.1 criteria
			Age ≥ 18
			Pulse oximetry of >95% on room air in patients with previous radiation therapy
			ECOG score of ≤ 2 or Karnofsky score of ≥ 50.
			Bilirubin ≤ 2 x upper limit of normal
			Creatinine ≤ 2x upper limit of normal for age
			AST ≤ 3x upper limit of normal
			Hgb ≥ 7.0 g/dl (transfusion allowed)
			Off investigational therapy for 1 month prior to receiving treatment on this study.
			For entry into Groups B or C patients must be off conventional therapy for at least 1 week prior to receiving treatment on this study.
			Informed Consent explained to, understood by and signed by patient. Patient given copy of informed consent.
			Due to unknown effects of this therapy on a fetus, pregnant women are excluded from this research. The male partner should use a condom. Females of child-bearing potential must be willing to utilize one of the more effective birth control methods during the study unless female has had a hysterectomy or tubal ligation.

PATIENT ID_____**PATIENT NAME**_____

TUMOR CTL PROTOCOL (TREATMENT)

YES	NO	
Any "**YES**" answers will make a patient **ineligible** for study participation.		
		Severe intercurrent infection
		Receiving systemic corticosteroids (patients off steroids for at least 48 hours are eligible)
		Pregnant
		HIV positive

Signature of MD_____**Date**_____

To check eligibility of a patient, telephone Dr. Musher at 713-798-3750. To register a patient, telephone the Center for Cell and Gene Therapy research coordinator at 832-824-4594

2.0 OBJECTIVES

Primary endpoint

2.1 To determine the safety of up to 6 intravenous infusions of multiTAA-specific T cells in pancreatic cancer patients with metastatic, locally advanced unresectable, or resectable disease.

2.2 To determine the feasibility of completing a total of 6 intravenous infusions of multiTAA-specific T cells to pancreatic cancer patients with metastatic, locally advanced unresectable, or resectable disease.

Secondary endpoint

2.3 To evaluate the progression-free and overall survival of patients after multiTAA-specific T cell infusions

Tertiary endpoints

2.4 To obtain information on the expansion, persistence and anti-tumor effects of the adoptively-transferred TAA-specific T cells

2.5 To determine whether multiTAA-specific T cell infusion enables recruitment of the patients' endogenous immune system as measured by epitope/antigen spreading

3.0. BACKGROUND AND RATIONALE

3.1 Targeting EBV-associated malignancies using adoptively transferred T cells

The adoptive transfer of antigen-specific T cells has proven safe and effective when used to prevent and treat a range of virus-associated malignancies including EBV-associated post- transplant lymphoproliferative disease (PTLD), nasopharyngeal cancer (NPC) and EBV-associated Hodgkin (HL) and non-Hodgkin lymphoma (NHL).

3.2 Adoptive immunotherapy for non-viral tumors

More recently we have extended the scope of our immune-based therapies to include non-viral tumor associated antigens (TAAs). From an immunotherapeutic perspective the model tumor antigen is one that is exclusively and universally expressed on tumor cells and ideally should be essential for the maintenance of the oncogenic phenotype of the tumor. However, the majority of antigens do not meet these criteria since they are not neo-antigens uniquely present in malignant cells but rather antigens that are also expressed in normal cells and against which peripheral blood T cells are tolerized or deleted. Tumor-specific antigens have nonetheless been identified, and these can be classified into 4 groups;

(i) Unique antigens (eg. MUM1) result from single mutations that are tumor- and patient-specific and therefore are only expressed in neoplastic cells[1-3]. They are often considered ideal for immunotherapy since tumors can be specifically targeted without destroying nearby normal tissue[1-4]. However, because they are also usually patient-specific, the identification of the mutatedgene and then the generation of an individualized T cell product targeting the identified antigen is highly labor and cost intensive.

(ii) Shared lineage-restricted antigens are expressed on tumors as well as their normal tissue of origin and include the melanoma-associated antigens MART, gp100 and Melan-A. These antigens are strongly immunostimulatory enabling the efficient and relatively simple generation

and expansion of tumor-specific T cells from healthy donors and patients with minimal *in vitro* manipulation[5]. However, T cell-mediated destruction of normal melanocytes, for example, has resulted in vitiligo as well as ocular and systemic autoimmunity in patients treated with melanoma-specific T cells or tumor infiltrating lymphocytes (TILs)[6].

(iii) Shared tumor-specific TAA (e.g. the cancer testis antigens [CTA] - MAGE, BAGE, GAGE, NY-ESO-1, SSX, PRAME) are expressed in multiple tumors including pancreatic cancer but not in healthy organs[7-15], with the exception of germ line tissues that are immune privileged and therefore not susceptible to T cell attack. Most CTAs have heterogeneous expression in cancer tissues and are frequently expressed in high-grade or late tumor stages, with expression often correlated with a worse prognosis. Furthermore, tumors expressing one often express multiple CTAs, and several have been found to be targets of spontaneous humoral or cell-mediated immune responses[16-18]. Thus, CTAs are particularly attractive as targets for tumor immunotherapysince reactive T cells can be produced on a large scale to provide broad-spectrum protection against a variety of tumors. CTAs have been targeted in both vaccine and T cell therapy protocols,with evidence of clinical efficacy[19-25].

(iv) The last group of antigens are over expressed in many different tumors but expressed at low levels in healthy tissue (eg. hTERT, CEA and Survivin). T cells targeted to these antigens carry the risk of inducing collateral damage to normal tissues co-expressing the antigen (e.g. CEA and normal biliary epithelium), and there are limited clinical data available regarding the safety of targeting these antigens *in vivo*. However, Survivin- and CEA-specific T cells have been isolated from the peripheral blood of patients who have cleared their tumors, and increases in Survivin-specific T cells in patients receiving oncolytic viruses have been reported, suggesting that theycan have efficacy without toxicity in patients[26-31].

3.3 Clinical experience targeting non-viral TAAs

3.3.1 Melanoma-targeted therapies

T cell immunotherapies for non-viral tumor antigens have been described, with promising clinical results in some studies. Rosenberg and colleagues have long used melanoma-specific TILs, which include specificities directed to both CTAs/shared lineage antigens and neoantigens, to treat metastatic melanoma [32-34]. Indeed, in a review of 93 patients with metastatic melanoma refractory to standard therapies, the administration of highly selected, TIL-derived, tumor-reactiveT cells and high-dose IL-2 (720,000 IU/kg q 8h to tolerance) in conjunction with immunodepleting chemotherapy -/+ total body irradiation produced objective clinical responses to treatment in 52 patients (39 PR, 12 CR), including regression of large bulky tumors[35,36]. These results have been recapitulated by others using selectively activated and in vitro expanded T cells melanoma- targeted T cells[37,38,39,40].

3.3.2 T cell therapy to prevent leukemic relapse

Adoptive immunotherapy has also proven to be an effective strategy in preventing leukemic relapse in the allogeneic hematopoietic stem cell transplant (HSCT) setting. The first clinical trials involved the administration of donor peripheral blood [donor lymphocyte infusions (DLI)], which contained T cells that were able to mediate antitumor activity in vivo[41]. However, the increased risk of graft versus host disease (GVHD) due to the presence of relatively high numbers of cells with alloreactive potential led subsequently to the study of selectively-expanded T cell populationsas an alternate therapeutic option. To date, the antigens targeted can be divided into 2 categories:

(i) minor histocompatibility antigens (mHAgs) expressed by leukemia progenitors, and (ii) TAAs overexpressed by the leukemic cells with limited expression on normal cells.

(i) mHAgs are HLA-binding peptides derived from endogenous proteins in cells of the HSCT recipient that differ from those of the donor due to genetic polymorphisms. As such they represent a unique class of antigens that can only be targeted after allogeneic HSCT to promote both graft vs leukemia (GVL) and GVHD effects in vivo.[42] Warren and colleagues evaluated the safety of adoptively transferring donor-derived CD8+ clones recognizing mHAgs preferentially expressed on hematopoietic cells to

patients with relapsed acute leukemia after myeloablative allogeneic HSCT[43] at cell doses ranging from 2.25 - 6.6 x 10^9 cells. Pulmonary toxicity was seen in 3 of the 7 treated patients, and was severe in one, and correlated with the level of expression of the mHAg-encoding genes in lung tissue. However, the administration of steroids coincided with a rapid reversal in pulmonary symptoms[43].

(ii) In both the autologous and donor-specific setting adoptive transfer approaches are being developed against a number of leukemia-associated antigens including Wilms Tumor Gene 1 (WT1), Proteinase 3 (Pr3), human neutrophil elastase (NE), melanoma associated antigen A3 (MAGE-A3) and preferentially expressed antigen in melanoma (PRAME)[17,18]. Of these WT1 is perhaps the most extensively characterized and its clinical relevance is evidenced by the fact that disease control or remission in several vaccine studies has been associated with the induction of WT1-specific T cells. O'Reilly and colleagues have initiated a clinical trial of donor-derived WT1 peptide- specific T cells, activated using DCs loaded with an overlapping peptide library (15mers overlapping by 11 amino acids) spanning the entire sequence of the antigen, and infused as treatment of persistent minimal residual disease or recurrence of WT1+AML, ALL, or MDS following allogeneic HSCT. In preliminary reports T cell infusionsat the lowest dose levels were reported to be safe, well tolerated, and associated with clinical benefit[44,45].

3.4 Targeting lymphoma, myeloma and solid tumors using tumor-targeted T cells

To use an adoptive immunotherapeutic approach to treat patients with hematologic malignancies (lymphoma and multiple myeloma) and solid tumors we developed a protocol for the in vitro generation of T cell lines targeting the TAAs Survivin, PRAME, MAGE-A4, NY-ESO-1 and SSX2, which are expressed in a range of tumors. The multi-antigen-targeted (multiTAA) T cells were generated using dendritic cells (DCs) loaded with pepmixes (overlapping peptide libraries) spanning the 5 target antigens.

Lymphoma: To date, 20 patients with lymphoma have been infused with multiTAA T cells without adverse events. Nine patients were treated for active disease. Of these, 2 patients had transient disease stabilization (5mo), 2 patients have stable disease (3mo ongoing), and 5 patients (3 HL, 1 DLBCL, 1 composite lymphoma) achieved durable complete remissions by PET, without additional therapies. These clinical responses correlated with a progressive increase in the frequency of tumor-specific T cells directed against both targeted and non-targeted TAAs, indicating that the infused T cells induced localized in vivo inflammation, resulting in endogenousT cell activation and antigen/epitope spreading. A further 11 patients were infused as adjuvant therapy. Of these, all but 2 remain in remission (median 17 months postinfusion, range 6-34 months) - a benefit likely due to the infused cells as the best prior response in these patients produced remissions lasting a median of only 4 months (range 1-6 months). These data support both the safety and clinical benefit of autologous multiTAA T cells as adjuvant therapy forlymphoma patients.

Myeloma and solid tumors: We subsequently extended this approach to other malignancies andto date we have infused 7 patients with multiple myeloma and 5 patients with solid tumors (1 squamous cell carcinoma, 1 lung cancer, and 3 osteosarcoma) with a similar safety.

3.5 Extending our approach to treat pancreas cancer

Given our demonstration that (i) targeting NY-ESO-1, PRAME, MAGE-A4, SSX2 and Survivin simultaneously is feasible and safe, and (ii) these antigens are expressed in pancreatic cancer, we now propose a clinical trial of multiTAA-specific T cells in patients with pancreatic cancer[13,15,46,47]. The T cell generation protocol will be identical to that used in our lymphoma, myeloma and solid tumor studies. In the current pilot study, we propose testing the antitumor activity of multiTAA-specific T cells administered at a fixed dose of 1x10^7 cells/m^2.

3.6 Potential adverse events

Although no toxicity has been associated with multiTAA-specific T cells to date, we will actively look for evidence of potential side effects such as:

Cytokine Release Syndrome:

There have been several reported SAEs associated with cytokine release syndrome (CRS) in patients who received T cells[48] or bispecfic T-cell engagers[49]. The majority of CRS have been reported after the infusion of CAR T cells[50-52], but CRS can also occur after the infusion of conventional antigen-specific T cells[53] or tumor infiltrating lymphocytes[54]. Patients will be monitored closely as per study calendar and assessed for evidence of incipient CRS (onset of fever, malaise and dyspnea) and treated promptly. Management of CRS will follow published guidelines[48,55], and is described in more detail in SOP F 05.11.XX and includes treatment options based on the clinical severity of the symptoms, such as oxygen, inotropic agents, IL-6 receptor antibody (4-8 mg/kg), TNF-α antibody (5-10 mg/kg), and/or steroids (1-2 mg/kg/day of methylprednisolone or equivalent).

Pancreatitis:

There have been reports of pancreatitis in patients who received t-cells on this study. A relationship between pancreatitis and pancreatic cancer is established, and may represent a normal overlap of pathology between the two conditions. Pancreatitis that occurs in the setting of pancreatic cancer could be via obstructive etiology from the primary or regionally metastatic tumors. Pancreatitis can also commonly relate to infectious processes in patients treated with pancreatic cancer, particularly as the duct system can provide an ideal reservoir for bacteria to accumulate. Based on the relationship between pancreatitis and pancreatic cancer we consider it more likely that the development of pancreatitis in patients who received t-cells is related to the cancer as opposed to the t-cell treatment however we cannot rule out the possible role of the t- cells in this process.

4.0 PATIENT ELIGIBILITY

4.1 Procurement Inclusion Criteria

4.1.1 Any patient with biopsy proven pancreatic adenocarcinoma.

4.1.2 Patients with life expectancy $\geq$ 6 months.

4.1.3 Age $\geq$18 years

4.1.4 Hgb ≥7.0 g/dl (transfusions allowed),

4.1.5 Informed Consent explained to, understood by and signed by patient. Patient given copy of informed consent.

4.2 Procurement Exclusion Criteria

4.2.1 Patients with severe intercurrent infection.

4.2.2 Patients with active HIV infection (can be pending at this time)

4.3 Treatment Inclusion Criteria

4.3.1 Any patient with biopsy-proven pancreatic adenocarcinoma:
Group A: Patients with locally advanced or metastatic pancreatic adenocarcinoma who experienced a documented best response of investigator-assessed confirmed PR or SD per RECIST v1.1
Group B: Patients with locally advanced or metastatic pancreatic adenocarcinoma who experienced progressive disease following first line chemotherapy or who are judged by the investigator as being ineligible to receive standard of care chemotherapy
Group C: Patients with potentially resectable pancreatic cancer who have completed planned preoperative neo-adjuvant chemotherapy, radiotherapy or combination chemoradiation

4.3.2 Patients must have measurable or evaluable disease per RECIST 1.1 criteria.

4.3.3 Patients with life expectancy ≥12 weeks

4.3.4 Age ≥18

4.3.5 Pulse oximetry of >95% on room air in patients who previously received radiation therapy

4.3.6 Patients with an ECOG score of ≤ 2 or Karnofsky score of ≥ 50 as described below:

ECOG Performance Status	
Grade	ECOG
0	Full active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Performance Status Criteria	
Karnofsky performance scores are intended to be multiples of 10	
Karnofsky Score	Description
100	Normal, no complaints, no evidence of disease

90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or do active work.
60	Required occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.

4.3.7 Patients with bilirubin $\leq$2x upper limit of normal, AST $\leq$3x upper limit of normal, Hgb ≥7.0 g/dl (transfusion allowed).

4.3.8 Patients with a creatinine $\leq$2x upper limit of normal for age

4.3.9 Patients should have been off other investigational therapy for one month prior to receiving treatment on this study.

4.3.10 For Groups B or C patients must be off conventional therapy for at least 1 week prior to receiving treatment on this study.

4.3.11 Informed Consent explained to, understood by and signed by patient. Patient given copy of informed consent.

4.3.12 Due to unknown effects of this therapy on a fetus, pregnant women are excluded from this research. The male partner should use a condom. Females of child-bearing potential must be willing to utilize one of the more effective birth control methods during the study unless female has had a hysterectomy or tubal ligation.

4.4 Treatment Exclusion Criteria

4.4.1 Patients with severe intercurrent infection.

4.4.2 Patients receiving systemic corticosteroids (Patients off steroids for at least 48 hours are eligible)

4.4.3 Pregnant

4.4.4 HIV positive

5.0 STUDY DESIGN

This protocol will be discussed with eligible patients and informed consent for participation in the study will be obtained for the generation of the cell lines. The protocol will be discussed with patients undergoing treatment at other medical Institutions at the time they are referred to Houston Methodist Hospital (HMH).

All cell culture manipulations will be carried out in the Center for Cell and Gene Therapy GMP facility using current standard operating procedures (SOPs). After quality assurance testing of the manufactured cell product is complete, a certificate of analysis will be issued.

5.1 Blood procurement for multiTAA T cell and APC generation

Generation of multiTAA T cells requires the generation of several different components from peripheral blood mononuclear cells (PBMC). The line will be derived from patient PBMCs, by stimulation with antigen presenting cells (APCs) pulsed with pepmixes spanning the TAAs SSX2, MAGEA4, Survivin, PRAME, and NY-ESO-1. The initial stimulation will be performed in the presence of the Th1/pro-proliferative cytokines interleukin (IL) 7, IL12, IL15, and IL6 and cells will be expanded in the presence of IL2 or IL15. The APCs used to stimulate and expand the tumor-specific T cells will be DCs derived from patient mononuclear cells.

For T cell generation, we will collect either:
* a unit of blood (~450ml) (for patients with ALC of >500) or
* a maximum blood draw of 450 ml peripheral blood obtained in 1-3 draws over a two month period for CTL generation, testing for infectious viruses and HLA typing. PBMCs will be separated from whole blood using ficoll gradients. T cells and monocyte-derived dendritic cells (DCs) can be prepared from fresh or cryopreserved PBMC.

To initiate multiTAA T cells we will make DCs by culture of PBMC-derived monocytes with cytokines (GM-CSF, IL-4) followed by maturation with a standard DC maturation cocktail (IL-1β, IL6, TNFα and PGE1). These mature DCs will be pulsed for 30-60 mins with a mastermix of pepmixes spanning the target antigens PRAME, SSX2, MAGEA4, NY-ESO-1 and Survivin. For dilution 1ul of each pepmix (200ng/peptide) will be added to 200ul Cell Genix/RPMI media and 50-100ul will be used to pulse the DCs (≤5x10e6 DCs - 50ul; >5x10e6 DCs - 100ul). Subsequently the DCs will be washed once and used to stimulate PBMC-derivedT cells in the presence of a T cell activating cocktail, IL7, IL15, IL12 and IL6 at a responder:stimulator ratio of at least 10:1. For initiation, DCs will be prepared from peripheral blood and the T cells will be derived from the monocyte-depleted PBMC fraction.

To expand the tumor-specific T cells we will use pepmix-pulsed DCs for the second and subsequent stimulations and cells will be cultured in the presence of IL2 or IL15.

At the end of the culture period, multiTAA T cells will be cryopreserved and aliquots tested for phenotype, function, specificity, identity and sterility. The frequency of tumor-specific T cells will be determined using intracellular cytokine staining, ELIspot assay, and/or HLA multimers, if available. Effector memory phenotype and T cell subsets will be analyzed by flow cytometry.

Products that meet study specific release criteria, as detailed on the COA, will be infused as per Section 5.2.

If a positive sterility testing result is reported after the product is infused, the FDA and other relevant parties will be notified as per manufacturing SOP B01.03.XX (Product Quality Assurance Program and Release and Return of Clinical GMP/GTP Products) and clinical research SOP J02.06.XX (Serious Adverse Experience and Unanticipated Problem Reporting). Our management of such a situation is further described in our SOP F05.09.XX (Management of CulturePositive Cell Therapy Products).

We will use pepmixes produced by JPT Technologies as an antigen source. These pepmixes are overlapping peptide libraries (15 mers overlapping by 11 amino acids) spanning the entire sequence of each of the antigens of interest as per our lymphoma (TACTAL), myeloma (TACTAM), and solid tumor (TACTASOM) studies.

5.2 Administration and Monitoring

Three disease groups will be studied.
Group A: Patients with locally advanced or metastatic adenocarcinoma who are responding (defined as stable disease or tumor volume reduction) following 3 cycles of first line chemotherapy will be evaluated in the clinic and receive 6 infusions with a fixed dose of multiTAA T cells starting on chemotherapy cycle 4 and occurring on the 4th week of the cycle, which is a chemotherapy “off” week.

Group B: Patients with locally advanced or metastatic adenocarcinoma who have failed first line chemotherapy or are intolerant or ineligible to receive standard of care chemotherapy will be evaluated in the clinic and receive 6 infusions (administered at monthly intervals) with a fixed dose of multiTAA T cells.

Group C: Patients with resectable pancreatic adenocarcinoma following completion of neoadjuvant chemotherapy, radiotherapy or combination. These patients will receive 6 infusions with a fixed dose of multiTAA T cells. One infusion will occur 4 weeks prior to surgical resection (with an option to infuse up to one week earlier) and after the completion of all pre-operative chemotherapy and/or radiation. The subsequent 5 infusions will occur at monthly intervals beginning 8 weeks post-surgery.

Monitoring: Patients will be monitored for clinical toxicity by the CTEP NCI Common Toxicity Criteria Scale (Version 4.X, See Section 12.3) with the exceptionof CRS toxicities that are related to T cell infusions. CRS toxicities will be graded according to Appendix I. We will also analyze immunological parameters including T cell frequencies by ELIspot and multimer studies in patients who have HLA typesfor which multimers are available. Functional analyses (antigen-specific cytotoxicity and cytokine release) will be performed by chromium release assays and ELIspot/intracellular cytokine staining, respectively. The levels of serum cytokines before and following infusion will be compared. A time period of 4 weeks post the 1st infusion will constitute the time for clinical efficacy and safety monitoring. Thereafter patients will receive 5 additional infusions of cells at the same cell dose (or below the patient’s original dose can be administered) at monthly intervals. Patients that undergo surgical resections (Group C) will receive1 infusion prior to surgery and 5 additional infusions of cells at the same cell dose (or below the patient’s original dose can be administered) at monthly intervals aftersurgery.

6.0 TREATMENT PLAN

This study will evaluate the clinical safety and look for evidence of benefit associated with the administration of tumor-targeted T cells in a fixed dose study.

6.1 Dosage

Patients will receive 6 infusions of multiTAA T cells at a fixed dose of $1x10^7$ cells/m^2.

6.2 Dose Schedule

This protocol is designed as a pilot fixed-dose study.

Each patient will receive 6 infusions of multiTAA T cells at a fixed cell dose (1 x 10^7 cells/m^2) within the same week at the times specified in the study calendar. The expected volume of infusion will be 1 to 10 cc.

6.3 Patients may be premedicated with diphenhydramine (Benadryl) up to 1mg/kg IV (max 50mg) and acetaminophen (Tylenol) 10mg/kg po (max 650mg), though this is not mandatory.

6.4 Cell Administration: Tumor-specific T cells will be given by intravenous injection over 1-10 minutes through either a peripheral or a central line.

6.5 Monitoring will be undertaken according to institutional standards for administration of blood products with the exception that the injection will be given by a physician.

6.6 Patients will receive supportive care for acute or chronic toxicity, including blood components or antibiotics, and other intervention as appropriate.

6.7 All treatments will be administered at the Center for Cell and Gene Therapy in Houston Methodist Hospital. Patient follow up and regular care will be at the Dan L. Duncan Cancer Center at Baylor Clinic or Smith Clinic.

7.0 PATIENT EVALUATION

7.1 Follow-up Interval

Patients shall be seen in clinic prior to each T cell infusion and evaluated (seen in clinic or contacted by research coordinator) at 1 and 2 weeks after each infusion, week 4, 6, and 8 after the last infusion and then at 3, 6, 9 and 12 months after the last infusion. Study-related blood draws will cease 12 months after the last T cell infusion but we will then continue to follow patients clinically for up to 4 additional years (total of 5 years follow-up) to evaluate long-term disease responses. If persistence of cells is noted at the 12 month visit, additional follow up will be added. Additional visits will be obtained as clinically indicated.

7.2 A complete history and physical examination is necessary prior to administration of multiTAA T cells. Medical history will be obtained at every follow-up visit and will be reviewed annually for 5 years.

7.3 Other Studies

7.3.1 The following investigations will be obtained at the time points specified in the study calendar:
CBC and differential, BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO2, albumin and total protein, and CA19-9.

7.3.2 Pregnancy testing (blood) is required on female patients of childbearing potential prior to multiTAA T cell infusion #1.

7.3.3 Diagnostic imaging (CT scans, MRI, nuclear imaging) and/or blood tests (serum cytokines) to document measurable disease and response to therapy prior to the first infusion and every 2-3 months thereafter for up to1 year after the last infusion, as per standard clinical care monitoring for patients with pancreatic cancer. The time may vary by 1-2 weeks due to scheduling issues and may be done earlier if clinically indicated. If diagnostic imaging studies are performed at other times either during or after treatment on this study, that data will be collected and information gained will be used for this study.

7.3.4 The following investigations will be obtained at the time points specified in the study calendar. 20-40ml of peripheral blood will be collected in preservative-free heparin.. This blood will be used for analysis of specificity of multiTAA T cell response using HLA multimer analysis and immune function assays including ELIspot, intracellular cytokine staining and cytotoxicity assays. Serum will be batched for analysis of blood cytokine levels. These studies will be done on patients on whom the appropriate reagents are available.

7.3.5 Study specific blood tests will cease 12 months after the last T cell infusion but we will continue to follow patients clinically once a year for up to 4 additional years (total of 5 years follow-up) to evaluate long term disease responses.

7.3.6 Other Tissues: Should the patient undergo a tumor biopsy/surgical resection at any time while they are on study, a sample of this will be used to assess the tumor antigen expression profile and to look for evidence of T cell infiltration.

7.3.7 If a patients' hemoglobin is <7.0g/dl at any of the evaluation times, the amount of blood drawn for the evaluation will be reduced and may be obtained over more than one venipuncture, if necessary.

7.4 Summary of Monitoring

Group A Study week	Pre-Infusion	Treatment	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11
Events			SOC	SOC	SOC		SOC	SOC	SOC		SOC	SOC	SOC
T cells		x				x				x			
History	X		x	x		x	x	x		x	x	x	
Physical	X					x				x			
CBC/diff	X					x				x			
BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO_2, albumin, total protein, CA 19-9[$]	X					x				x			
Imaging[^]	X												
Immune Function[⊥]	X		x	x		x	x	x		x	x	x	
Pregnancy test[#]													

Group A Study week	Wk12	Wk13	Wk14	Wk15	Wk16	Wk17	Wk18	Wk19	Wk20	Wk21	Wk22*
Events		SOC	SOC	SOC		SOC	SOC	SOC		SOC	SOC
T cells	x				x				x		
History	x	x	x		x	x	x		x	x	x
Physical	x				x				x		
CBC/diff	x				x				x		
BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO_2, albumin, total protein, CA 19-9[$]	x				x				x		
Imaging[^]											
Immune Function[⊥]	x	x	x		x	x	x		x	x	x
Pregnancy test[#]											

Group B Study week	Pre-Infusion	Treatment	Wk 1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11
T cells		x				x				x			
History	X		x	x		x	x	x		x	x	x	
Physical	X					x				x			
CBC/diff	X					x				x			
BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO_2, albumin, total protein, CA 19-9[$]	X					x				x			
Imaging[^]	X												
Immune Function[⊥]	X		x	x		x	x	x		x	x	x	
Pregnancy test[#]	X												

Group B Study week	Wk12	Wk13	Wk14	Wk15	Wk16	Wk17	Wk18	Wk19	Wk20	Wk21	Wk22*
T cells	x				x				x		
History	x	x	x		x	x	x		x	x	x
Physical	x				x				x		
CBC/diff	x				x				x		
BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO_2, albumin, total protein, CA 19-9[$]	x				x				x		
Imaging[^]											
Immune Function[⊥]	x	x	x		x	x	x		x	x	x
Pregnancy test[#]											

Group C Study week	Pre-Infusion	Treatment[&]	Wk1	Wk 2	Wk 3	Wk4	Infusion #2[%]	Wk1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7
Events						Surgery		SOC	SOC	SOC		SOC	SOC	SOC
T cells		x					x				x			
History	X		x	x			x	x	x		x	x	x	
Physical	X						x				x			
CBC/diff	X						x				x			
BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO_2, albumin, total protein, CA 19-9[$]	X						x				x			
Imaging[^]	X													
Immune Function[⊥]	X		x	x			x	x	x		x	x	x	
Pregnancy test[#]	X													

Group C Study week	Wk8	Wk9	Wk10	Wk11	Wk12	Wk13	Wk14	Wk15	Wk16	Wk17	Wk18*
Events		SOC	SOC	SOC							
T cells	x				x				x		
History	x	x	x		x	x	x		x	x	x
Physical	x				x				x		
CBC/diff	x				x				x		
BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO_2, albumin, total protein, CA 19-9[$]	x				x				x		
Imaging[^]											
Immune Function[⊥]	x	x	x		x	x	x		x	x	x
Pregnancy test[#]											

Generic Long term follow-up Table

Study timepoint (**after last infusion**)	Wk4	Wk6	Wk8	Mth 3, 6, 9, 12	Yr 2, 3, 4, 5
T cells					
History	x	x	x	x	x
Physical					
CBC/diff					
BUN, creatinine, bilirubin, SGOT, SGPT, alkaline phosphatase, Na, K, Cl, CO_2, albumin, total protein, CA 19-9[$]					
Imaging[^]					
Immune Function[⊥]	x	x	x	x	
Pregnancy test[#]					

SOC = Standard of care
* Following this study time point monitoring will be performed per long term follow-up Table
& For Group C the 1st infusion occurs at 4 weeks prior to surgery with a provision to infuse up to 1 week earlier to allow for variations in surgery scheduling.
% For Group C the 2nd infusion will occur 8 weeks post-surgery
^See Section 7.3.3. Imaging studies can be performed within 8 weeks of T cell administration and post-infusion monitoring will be per standard of care
⊥ See Section 7.3.4
See Section 7.3.2
$ Or any other serum tumor marker that is elevated because of the pancreatic tumor (such as CEA or CA-125)

8.0 RESPONSE CRITERIA

A 4-week period after the first infusion will constitute a course, which will be evaluated for critical toxicity.

Patients with measurable disease will be assessed by standard criteria to determine clinical response. Evaluations of tumor size will be performed pre-infusion and approx. every 2-3 months thereafter as per standard clinical care patient monitoring. All patients who receive multiTAA T cells and continue to be enrolled on the study will be evaluable for response. Patient long term overall and progression free survival will also be evaluated at 1 year and then annually for up toan additional 4 years (total of 5 years follow-up).

8.1 Definitions

This study will use the RECIST 1.1 criteria

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm with CT scan, MRI, or clinically using calipers. The investigator will identify up to 5 measurable lesions to be followed for response. Serial measurementsare to be done with CT or MRI. The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up.

Complete Response: Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design Synopsis

This study is designed as a fixed-dose pilot study to evaluate the safety and feasibility (primary endpoints), and efficacy (tertiary endpoint) of up to 6 intravenous infusion of multiTAA-specific T cells in pancreas cancer patients with metastatic, locally advanced unresectable, or resectable disease.

In each disease group, the sample size is a maximum of 15 patients who receive at least one infusion of multiTAA-specific T cells. The total sample size of the study will be a maximum of 45.

We expect to enroll 15-20 patients per year and therefore expect the study to conclude accrual within the estimated period of 36 months.

Treatment-related serious adverse events (tSAE) are defined as grade III-IV CTCAE toxicity or grade 3-4 CRS toxicities that are determined to be related to T cells.

9.2 Sample Size Determination and Trial Monitoring

In each of the disease groups, the primary goals are to study the safety of multiTAA-specific T cells and determine the feasibility of administering 6 infusions of cells.

To assess the safety of multiTAA-specific T cells: The sample size is 15 patients in each disease group, calculated based on the considerations as follows. To study whether there are excessive treatment-related serious adverse events (tSAE), a tSAE rate of 20% is considered excessive (corresponding to the alternative hypothesis), while a rate below 20% is considered acceptable. Based our previous experience with T cell therapy, we anticipate at most 1.5% rate (corresponding to the null hypothesis). The monitoring rule is that if more than one tSAE is observed, then the treatment is considered unsafe and the accrual to the trial will be halted forthat disease group.

Under the alternative hypothesis that the true tSAE rate is 20%, then the probability of observing more than one tSAE event out of 15 patients is 83.3% (statistical power for rejecting the null hypothesis, based on the exact binomial distribution). Under the null hypothesis that the true tSAE rate is 1.5%, the probability of observing more than one tSAE event out of 15 patients is only 2.08% (type I error for rejecting the null hypothesis, based on the binomial distribution).

There will be no formal interim analysis of safety but we will employ an ad hoc monitoring rule. The cumulative number of treatment-related serious adverse events will be counted for every 3 patients within each group. If there is more than 1 tSAE within a group, then the accrual to that group will be halted for excessive treatment-related serious adverse events. We will be looking at the data for at most 5 times for each group. Under the null hypothesis that the true tSAE rate is 1.5%, the probability of observing more than one tSAE event out of every 3, 6, 9, 12 and15 patients is 0.07%,0.32%,0.76%, 1.34% and 2.08%, respectively. The overall type I error is thus controlled at 4.57% level.

The total sample size is 45. If there is any death deemed possibly or probably related to multiTAA T cell infusion, the study will halt patient accrual for the respective disease group, and the data will undergo a thorough internal review and the outcome discussed with the FDA.

We employ a deterministic rule to assess the feasibility of giving 6 intravenous infusions of multiTAA-specific T cells: In each disease group the feasibility of completing all 6 infusions (henceforth called a series) will be monitored separately using a method similar to the 3+3 procedure. The cumulative number of successful completions of an infusion series will be accounted for every 3 patients. If at most one patient cannot finish the infusion series, then the trial will be allowed to accrue 3 additional patients. If after 6 patients, there are 2 or more patients who are unable to finish the infusion series, then the treatment strategy will be determined to be unfeasible but additional enrollments on that arm will continue.

9.3 Statistical Analysis

9.3.1 Safety Analysis of Toxicity and Adverse Event Data

All patients who receive at least one infusion of multiTAA-specific T cells will be included in the safety analysis. Patients will be monitored for clinical toxicity by the CTEP NCI Common Toxicity

Criteria Scale (Version 4.X, See Section 12.3) with the exception of CRS toxicities that are related to T cell infusions. CRS toxicities will be graded according to Appendix I.

Adverse event data and corresponding toxicity grades after T cell infusions and during long-term follow-up will be summarized in the form of tables. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be calculated.

Listings of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. Safety data will be summarized for each patient group and for all treated patients.

9.3.2. Analysis of anti-tumor activity, progression-free and overall survival data

Although tumor response and survival are not the primary endpoint of this trial, we will summarize tumor response by calculating overall response rates along with exact 95% binomial confidence intervals. Response will be evaluated as described in section 8.4. The progression-free and overall survival of patients will be summarized using the Kaplan-Meier method. The analysis will be done for each patient group and for all treated patients. We will also explore the relationship between the patient baseline characteristics and response as well as PFS/OS based on eth logistic model and the Cox regression methods, respectively.

9.3.3. Analysis of expansion and persistence of the adoptively-transferred TAA-specific T cells

Summary statistics such as mean ± SD, medians and ranges will be calculated at pre- and post-infusion time points to evaluate the T cell expansion and persistence based on the immunological parameters including phenotype and T cell frequencies by ELIspot and multimer studies, functional analyses (antigen-specific cytotoxicity and cytokine release) by chromium release assays and ELIspot/intracellular cytokine staining, and the levels of serum cytokines.

Changes in each of the immunological parameters from pre-infusion to each time point of post-infusion will be assessed and compared using paired t-tests, or when appropriate, the Wilcoxon signed ranks test. Paired comparisons of these T cells within a patient at each time point will also be performed. These analyses will be performed in each disease group and in the overall patient group.

Plots of growth curves will be generated to graphically illustrate patterns of T-cell expansion and persistence. Longitudinal modeling techniques such as the random coefficient mixed model will be employed to model each of the repeatedly-measured T cells. These models account for variation in individual-level intercepts and slopes over the follow-up time. Thus, we will be able to model proliferation of T cells over time and estimate the magnitude of expansion or decline of T cells. Correlations between frequencies of these immunological parameters at each time point of follow-up will be assessed using measures of correlation coefficients.

Alternative strategies to analyze these immunological parameters include calculation of area under the curve over time or piecewise longitudinal models based on apparent trends from plotsof growth curves. Despite the small patient numbers, a data-dense study will be generated dueto the repeat measurements on proliferation, immune function, and other parameters on each patient. The modeling strategies proposed here are amenable to these types of data but will however be considered exploratory and interpreted with caution due to limited study power. The

validity of the normality assumption on these data will be tested and appropriate transformations will be considered whenever indicated.

9.3.4. Analysis of Laboratory Data

Laboratory data, which includes CBC, BUN, creatinine, and liver function tests, will be examined in different ways. Descriptive statistics (means, standard deviations, medians and ranges) at pre-infusion, at weeks 1, 2, 4, 6, 8 and at months 3, 6, 9, and 12 post- T cell infusion will be calculated and summarized. A scatter diagram depicting laboratory values at each time point for each patient will also be generated. To analyze changes in laboratory values, a shift table with Stuart-Maxwell chi-square analysis of the change in the normal range from pre-infusion to post infusion time points (using high, normal, low) will be performed. When appropriate, these tables will be collapsed and the McNemar's test applied in place of the Stuart-Maxwell test. Diagnostic imaging (CT scans, MRI, nuclear imaging) and/or blood tests (serum cytokines) will be also summarized and plotted. These statistical analyses will be performed for each disease group and the overall patient group.

9.4. Stopping Guidelines

Statistical monitoring of grade III-IV CTCAE toxicity or grade 3-4 CRS toxicities related to T cells is employed. Safety guideline and the rule for halting the accrual will be implemented separately for each cohort. The guidelines serve as a trigger for consultation with the FDA for additional review, and are not formal "stopping rules" that would mandate automatic closure. Additionally, after consultation with the FDA, the PI can stop the study early.

In Group C, it is extremely unlikely that patients who receive their first T cell infusions will not undergo surgical resection since all imaging studies and a clinical plan will be determined prior to infusion and it is unlikely that the T cells will cause inflammation precluding/delaying subsequent surgical resection. The accrual to Cohort C will be halted if any patient experiences a delay in subsequent surgical resection due to toxicity related to the T-cell infusion and this issue will be discussed with the FDA to develop a plan. The plan would be submitted to the DRC and IRB prior to resuming accrual to Cohort C.

10.0 MODIFIED FOLLOW-UP AND OFF STUDY CRITERIA

10.1 Criteria for Modified Follow-Up

The following criteria will result in the patient being ineligible for further treatment on the protocol, although response data will continue to be collected as applicable.

10.1.1 Any patient who develops grade III-IV toxicity related to multiTAA T cells . In such patient the toxicities will be followed until resolution or until their off study date. Although no toxicity has been associated with the infusion of this product in patients with Hodgkin and non-Hodgkin lymphoma or multiple myeloma, we will actively look for evidence of any adverse events, such as cytokine release syndrome.

10.1.2 Any patient who receives any other hematopoietic cell product excluding blood or platelets. In such patients, adverse event data collection willcease.

10.1.3 Any patient who experiences Grade 3 or 4 cytokine release syndrome that persists beyond 72 hours. In such patients, the toxicity will be followed until resolution or until their off study date.

10.1.4 Any patient whose disease progresses (based on RECIST criteria) and who receives another therapy. In such patients, adverse event data collection will cease.

10.1.5 If the patient desires to discontinue treatment or if the physician feels thatit is in the best interest of the patient.

Patients who meet modified follow-up criteria remain on long-term follow-up as per the Summary of Monitoring (see table in Section 7.3.1)

10.2 OFF STUDY

10.2.1 Completion of study-specified procedures.
10.2.2 Refusal of study follow up by patient/Patient withdrawal of consent
10.2.3 Lost to follow up
10.2.4 Death

Any questions regarding patients on this study should be addressed to Dr. Musher at 713-798-3750.

11.0 RECORDS TO BE KEPT

The CAGT research nurse/coordinator will maintain a database documenting on study information, adverse events, off study notification and death information. The dates and doses of therapy as well as clinical chemistries, hematologic parameters, the clinical status and occurrence of any adverse events and subsequent interventions are to be kept on all patients.

Imaging reports
Surgical summaries
Autopsy summaries, where appropriate
Informed consent documents

All required clinical evaluation records will be the responsibility of Principal Investigator who will also be responsible for analysis of the clinical outcome and toxicity.

The laboratory evaluation of immunological efficacy will be the responsibility of Drs. Leen and Tzannou.

12.0 REPORTING REQUIREMENTS

12.1 Register all patients with Cell and Gene Therapy Research Coordinator.

12.2 Enter all patients by phoning Dr. Musher. The following data will be captured:

Eligibility
Pre-study
Concomitant Medication
Adverse event

CRS Adverse Event (if applicable)
Off study
Death

12.3 Drug Toxicity and/or Adverse Reactions

12.3.1 Toxicity Grading: The criteria listed in the CTEP (Version 4.X) of the NCI Common Toxicity Criteria Scale will be used in grading toxicity with the exception of CRS toxicities that are related to T-cell infusions. CRS toxicities will be graded according to Appendix I.

12.3.2 The CTEP CTCAE (Version 4.X) is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.3.3 Adverse events will be collected as per SOP J 02.05.XX and J 02.75.XX. Data on adverse experiences/toxicities regardless of seriousness, must be collected for documentation purposes only for 8 weeks after the last dosing of study drug/biologic.

12.3.4 Serious adverse events will be collected as per SOP J 02.06.XX.

13.0 INFORMED CONSENT

All patients must sign a document of informed consent consistent with local institutional and Federal guidelines stating that they are aware of the investigational nature of this protocol and of the possible side effects of treatment. Further, patients must be informed that no efficacy of this therapy is guaranteed, and that unforeseen toxicities may occur. Patients have the right to withdraw from this protocol at any time. No patient will be accepted for treatment without such a document signed by his or her legal guardian. Full confidentiality of patients and patient records will be provided according to institutional guidelines

14.0 CLINICAL TRIAL OVERSIGHT AND MONITORING

This protocol will be conducted in accordance with the Cell and Gene Therapy Monitoring Plan on file with the FDA.

This protocol will be monitored in accordance with the current Data Safety Monitoring Plan for investigator-initiated Phase I and II studies in the Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine.

The conduct of this clinical trial will be evaluated in accordance with Center for Cell and Gene Therapy Quality Assurance Policy and Procedure Plan.

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Appendix I - Grading of CRS

CRS Grading Scale

Grade	Symptoms
1	• Symptoms are not life threatening and require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, malaise)
2	• Symptoms require and respond to moderate intervention • Oxygen requirement <40% or hypotension responsive to fluids or • low dose of one vasopressor or Grade 2 organ toxicity
3	• Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40% or hypotension requiring high dose or multiple vasopressors or • Grade 3 organ toxicity or Grade 4 transaminitis
4	• Life-threatening symptoms • Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
5	• Death