THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

The Pre-emptive Use of Recipient-Derived Autologous CMV-Specific Cytotoxic T Cells for CMV Reactivation After Allogeneic Stem Cell Transplantation.
2013-0620

Core Protocol Information

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Full Title:	The Pre-emptive Use of Recipient-Derived Autologous CMV-Specific Cytotoxic T Cells for CMV Reactivation After Allogeneic Stem Cell Transplantation.
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Abstract

Objectives:

Primary
1. To assess the efficacy of recipient-derived autologous cytomegalovirus (CMV)-specific cytotoxic T cells (CTLs) as a pre-emptive therapy for CMV reactivation after allogeneic hematopoietic stem cell transplantation (HSCT) from a CMV negative donor.
2. To assess the non-relapse mortality with the use of recipient-derived autologous cytomegalovirus (CMV)-specific cytotoxic T cells (CTLs) as a pre-emptive therapy for CMV reactivation after allogeneic hematopoietic stem cell transplantation (HSCT) from a CMV negative donor.

Secondary
1. To assess the safety of the pre-emptive use of recipient-derived autologous CMV- specific CTL as a pre-emptive therapy for CMV reactivation after HSCT.
2. To assess functionality and persistency of infused autologous CMV-specific CTLs.

Rationale: (Be as concise as possible)

CMV is a B-herpesvirus that is very common in humans and leads to asymptomatic infection followed by viral persistence and latency. CMV is still one of the major causes of infectious complications after HSCT, although several new prophylactic options for CMV infection/disease have been made available. Among the recipients of HSCT, CMV causes pneumonia, gastroenteritis, and less commonly retinitis and hepatitis. Because of the initial high mortality of CMV pneumonia (80-90%), transplant physicians have long sought strategies to reduce its morbidity and mortality. CMV also exhibits an immunosuppressive

effect, which can lead to an increased susceptibility to invasive bacterial and fungal disease as well as graft versus host disease (GVHD) in selected clinical settings. Recent advances in diagnostic measures such as CMV antigenemia and polymerase chain reaction (PCR) and the introduction of effective antiviral agents have enabled sufficiently early detection of CMV to suppress reactivation and prevent subsequent development of CMV diseases (pre-emptive therapy).

The presence of CMV-specific T cell immunity has been reported to be an essential host factor in the control of infection and the recovery from CMV disease decades ago. However, restoration of T-cell immunity after HSCT is a slow process. The rebound of the thymus occurs late, particularly in adult patients, and the contribution of newly generated T cells during the first 6 months after transplantation may be negligible. Therefore, the initial protection against viruses has to come from the donor T cells co-infused with the graft or possibly from recipient T cells that have survived conditioning. This might leave some patients unprotected because no immunity is transferred when a patient receives a transplant of hematopoietic stem cells (HSCs) from a CMV-negative donor or umbilical cord blood (UCB) units that have T cells one log less than other donors and naive. Therefore, the use of adoptive immunotherapy with CMV-specific CTLs to restore the cellular immunity for CMV infections after HSCT has been investigated by many groups.

In HSCT, seropositive stem cell donors can usually serve as T cell donors and are available for T-cell donation. However, some seropositive donors may not consent, may be unavailable to provide T cells, or may not have enough antiviral memory T cells in their blood despite seropositivity. Furthermore, UCB recipients with delayed hematologic engraftment and immune reconstitution represent a unique group with high risk for viral infections but without the option of adoptive transfer of virus-specific CTL. Those groups of patients need to be investigated further for strategies that bypass the need to grow donor-derived CTL.

The protective role of recipient T cells after transplantation was not investigated in detail until recently because most transplantation protocols eradicate recipient T cells through a combination of the conditioning chemotherapy and an allogeneic effect of the graft. The notion that recipient T cells could survive even early after transplantation was supported by data from pediatric patient population undergoing UCB transplantation and showed that antigen-specific T lymphocytes of recipient origin were detected in patients receiving a transplant with a related donor, after a chemotherapy-based conditioning regimen, and who did not have GVHD(27). Recently, Chalandon et al showed when a T-cell depletion protocol was used that allowed recipient T cells to repopulate the T-cell compartment, the T cells maintained their function even after conditioning that includes total body irradiation. Furthermore, T cells appeared to protect the patient from CMV-related complications. These data support the notion to investigate the use of recipient-derived autologous CTLs for CMV reactivation after allogeneic HSCT especially for patients without the option to use donor-derived CTLs. Recently, Meij et al. showed the feasibility of generating patient-derived autologous CMV specific CTLs using IFNγ-capture system.

In conclusion, alternative strategies to provide safe and effective adoptive therapy for CMV reactivation after HSCT are needed especially in patients with CMV seronegative donors or following the use of UCB where there is no memory T cell response to CMV.

In this study, we will use this original and novel approach of infusing recipient-derived autologous CMV-specific CTLs for the treatment of CMV reactivation following HSCT in CMV seropositive patients.

Eligibility: (List All Criteria)

Inclusion:

1) STEP 1: Within 30 days of study entry: Patients with a history of bone marrow disorders including hematological malignancies and aplastic anemia, Myelodysplastic Syndrome (MDS) and Myeloproliferative disorder (MPD) planning to undergo allogeneic HSCT with reduced intensity or myeloablative conditioning regimens.

2) Disease status must be complete remission by standard criteria for Lymphoma and Acute Leukemia patients.

3) Patients with Myelodysplastic Syndrome (MDS) and Myeloproliferative Disorder (MPD) must have <5% blasts in the bone marrow.

4) Patients with T Cell ALL must be in complete remission and MRD negative (-) by flow cytometry and molecular studies.

5) Patients >/= 18 years of age.

6) Karnofsky greater than or equal to 80%.

7) CMV seropositive.

8) Donor is either matched related, matched unrelated, mismatched unrelated, or haploidentical. Cord blood recipients are also eligible.

9) Hgb greater than 10 g/L.

10) Patient or patient's legal representative, parent(s) or guardian able to provide written informed consent.

11) Negative pregnancy test in female patients of childbearing potential.

12) STEP 2: Eligibility at time of generating and infusing CMV-specific cytotoxic T cells (adoptive immunotherapy): CMV reactivation defined as CMV DNAemia >/= 137 copies/ml.

13) Evidence of neutrophil engraftment defined as the absolute neutrophil count (ANC)> 0.5 X 10^3/for 3 consecutive days.

14) Clinical status to allow tapering of steroids to less than 0.5 mg/kg/day prednisone or equivalent.

15) Negative pregnancy test in female patients of childbearing potential.

Exclusion:

1) STEP 1: Within 30 days of study entry: T cell leukemia or lymphoma.

2) CMV seronegative.

3) Positive for HIV, HBV, HCV, HTLV1 and/or HTLV2.

4) STEP 2: Eligibility at time of generating and infusing CMV-specific cytotoxic T cells (adoptive immunotherapy): Documented CMV end-organ disease.

5) Patients receiving ATG, or Campath within 28 days of CMV reactivation.

6) Patients with other uncontrolled infections. For bacterial infections, patients must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to generating CTLs. For fungal infections patients must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to generating CTLs. Progressing infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.

7) Patients who have received donor lymphocyte infusion (DLI) within 28 days.

8) Patients with active acute GVHD grades II-IV.

9) Active and uncontrolled relapse of malignancy.

Are patients <18 years of age eligible to participate in this study? ○ **Yes** ● **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

Studies that exclude children must have appropriate justification. Please select all that apply:

Phase II or III study with no Phase I data for the drug in pediatrics.

Please provide a letter from the Sponsor stating if a Phase I study planned for patients <18 years of age. (May include file attachment)

- This is a rare disease in pediatric patients
- Our Pediatric transplant program is very small
- Our sponsor does not allow pediatric patients to be included in this study.

Are participants >65 years of age eligible to participate in this study? ● **Yes** ○ **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Blood And Marrow Transplantation, Leukemia, Lymphoma

Treatment Agents/Devices/Interventions:

CMV-specific CTLs

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

Collection of peripheral blood mononuclear cells (PBMC) for manufacturing of CTLs
After enrollment, PBMC will be collected via venipuncture.
Venipuncture: up to 500 mL one time at the MD Anderson Blood Bank. The product will be cryopreserved for future use to generate CMV-specific CTLs.

PBMCs will be stored for 3 years. If the PBMCs are not needed to generate CTLs, they will be discarded.

Allogeneic HSCT and follow-up

1. Patients will undergo allogeneic HSCT per institutional guidelines.
2. CMV reactivation will be monitored by checking CMV DNA level by polymerase chain reaction (PCR).

Manufacture of recipient derived autologous CMV specific CTLs under GMP conditions

1. After documentation of CMV reactivation, defined as CMV DNA load is equal to or greater than 137 copies/ml, cryopreserved PBMC product of eligible patients' defined under "Eligibility" will be used for generation of CMV-specific CTLs.
2. Manufacture of recipient derived autologous CMV specific CTLs under GMP conditions will be performed at the MDACC GMP facility. Cryopreserved PBMC product from the recipient will be thawed, washed and diluted at 1 x 10^9 cells in 100 mL MACS GMP TexMACS Reagent (Miltenyi Biotec) for approximately 16 hours at 37°C (overnight). The product will then be stimulated with MACS® GMP Peptivator® HCMV pp65 (Miltenyi Biotec) for approximately 4 hours at 37°C, CO_2. Once incubation is completed the product will be washed and concentrated with TexMACS Reagent followed by an incubation with CliniMACS IFN-Gamma Catch Matrix Reagent (Cytokine-Secretion-System, Miltenyi Biotec). The stimulated cells will then be washed with CliniMACS buffer to stop stimulation reaction.

   After culture, magnetic enrichment of cytokine-secreting cells will be performed with the use of the CliniMACS Enrichment Reagent (Cytokine-Secretion-System) and the CliniMACS device (Miltenyi Biotec). CMV-specific T cells will be infused directly after the isolation procedure without any further in vitro expansion. The purity of the isolated pp65-specific T cells will be assessed by detection of IFN-γ+ cells in flow cytometry, with release criteria of $\geq$ 3% IFN-γ+T cells.

Administration and Monitoring of CTL infusion

1. Premedication for CTL infusion: acetaminophen up to 650 mg (or 10 to 15 mg/kg recipient weight) and diphenhydramine up to 50 mg (or up to 0.5 to 1 mg/kg recipient weight) should be given orally or IV prior to CTL infusion and may be repeated 4 hours later.
2. It is essential to avoid steroid as those may interfere with the efficacy of the infused CMV-specific CTLs. Steroids will be given only if the patient develops a severe or life threatening reaction to the infused CMV-specific CTLs.
3. CTL Administration: The CTL product will be given as single infusion within 72 hours of CMV reactivation.)
4. Patients will be monitored according to institutional standards for administration of blood products and at a minimum will be monitored according to below:
   - Patients should remain in the clinic for at least one hour.
   - Patients should remain on continuous pulse oximetry for at least 30 minutes.
   - Vital signs should be monitored at the end of infusion then at 30 and 60 minutes.
5. CTL dose infused will be at a maximum dose of 10e5 viable CD3+ T cells/kg.
6. The first three patients on protocol will be observed for at least 28 days for safety monitoring before more patients are enrolled in the study.

Supportive care

1. All patients should receive supportive care as clinically indicated.
2. It is essential to avoid steroid as those may interfere with the efficacy of the infused CMV-specific CTLs.
3. Steroids will be given only if the patient develops a severe or life-threatening reaction to the infused CMV-specific CTLs.

Initiation of anti-viral therapy

1. CMV viral load will be monitored at least weekly by PCR within the 28 days of autologous recipient-derived CMV-specific CTL infusion.

2. Indication to initiate anti-viral therapy will be determined by their response status as described in Table 4.

Table 4. Time-table for monitoring efficacy and initiation of anti-viral drugs

Monitoring	Day 5-7	Day 12-14	Day 19-21	Day 26-28
CMV DNA increase > 50% compared with baseline	X	X	X	X
CMV DNA >/= 5000 copies/ml	X	X	X	X
CMV DNA decrease < 50% compared with baseline			X	
CMV end-organ disease	X	X	X	X
X, indication to start anti-viral therapy				

Management of potential treatment toxicity

1. Microbial contamination of T-cell product.
   There is a potential that processing the T-cell product will inadvertently introduce microorganisms that could cause infection in the recipient after the cells are infused. Cultures of the T-cell product will be obtained to monitor for contamination. In the event that a microbial contamination is discovered after infusion of CTLs, standard GMP procedures will be followed.

2. Graft failure: Graft failure is initial neutrophil engraftment followed by subsequent decline in the ANC to < 500/mm3 for three consecutive measurements on different days, unresponsive to growth factor therapy that persists for at least 14 days in the absence of a known cause such as relapse. GF will be monitored as clinically indicated for the first 6 months after CTL infusion.

3. Graft Versus Host Disease (GVHD)
   The risk of GVHD following the infusion of recipient-derived autologous CTLs is expected to be low.

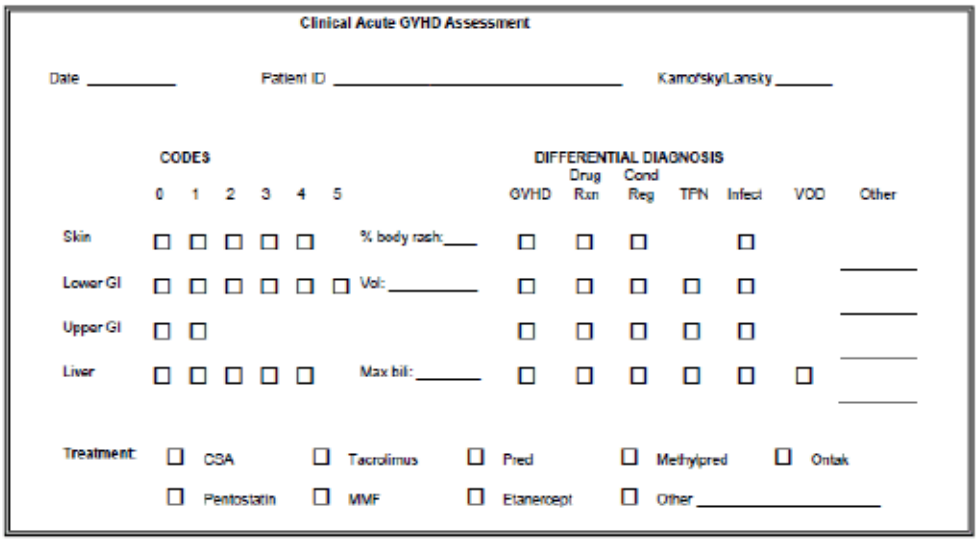
   GVHD organ stage scores, overall clinical grade, biopsy information for GVHD and relevant differential diagnosis will be recorded as clinically indicated. The score will encompass all information since the last assessment. Organ involvement, biopsy information, staging, differential diagnosis, and GVHD therapy will be documented in the medical record using the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) GVHD scoring stamp or equivalent.

   An example acute GVHD weekly data record (stamp) is shown below in Table 5.

Chronic GVHD

Patients developing sign/symptoms of chronic GVHD (CGVHD) as presented in Table 6 will have symptoms recorded on the CGVHD scoring form at the scheduled follow-up visits.

Table 5. GVHD assessment record



Clinical Acute GVHD Assessment

Date _____ Patient ID _____ Karnofsky/Lansky _____

	CODES						DIFFERENTIAL DIAGNOSIS						
	0	1	2	3	4	5		GVHD	Drug Rxn	Cond Reg	TPN	Infect	VOD	Other
Skin	☐	☐	☐	☐	☐		% body rash: ___	☐	☐	☐		☐		
Lower GI	☐	☐	☐	☐	☐	☐	Vol: _____	☐	☐	☐	☐	☐		
Upper GI	☐	☐						☐	☐	☐	☐	☐		
Liver	☐	☐	☐	☐	☐		Max bil: _____	☐	☐	☐	☐	☐	☐	

Treatment: ☐ CSA ☐ Tacrolimus ☐ Pred ☐ Methylpred ☐ Ontak
☐ Pentostatin ☐ MMF ☐ Etanercept ☐ Other _____

Other toxicities: Should unanticipated toxicities arise (e.g. severe local reactions or hepatorenal damage) they, too, will be graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.
Management of Toxicity. CTLs are susceptible to killing by steroids give at a dose of 1-2 mg/kg. This is standard therapy for GVHD and could also be given if a recipient develops other complications considered possibly related to CTL administration. In the case of GF, second allogeneic HSCT from the same donor or other is the only effective treatment. Other supportive care would be per standard medical practice.

Table 6. Definite and Possible Manifestations of Chronic GVHD

Organ System	Definite manifestations of chronic GVHD	Possible manifestations of chronic GVHD
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
GI tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia
GU	Vaginal stricture, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculoskeletal/ Serosa	Non-septic arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias
Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis

Correlative Studies
40 to 60 mL of blood will be taken pre-infusion, then 2 weeks, 4 weeks, 3 months, and 6 months post-infusion to measure CMV-specific T-cell frequencies, immunologic analysis, general immune reconstitution, and persistence of adoptively infused autologous CMV CTLs.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 105
Estimated monthly accrual at MDACC: 2

Accrual Comments:
Due to the randomness of the treatable CMV subsample size, which is binomial in q = .40 and n = number of patients initially enrolled and transplanted, up to 105 patients will be enrolled (21 months accrual) to ensure at least a 90% probability that there will be at least 36 patients with CMV.

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

Treatment and Primary Outcomes. This is a single-arm phase II trial of autologous virus specific CTLs for CMV reactivation in patients with hematologic malignancies (excluding T cell leukemia and lymphoma) undergoing CMV seronegative matched unrelated donor (MUD), mismatched unrelated or cord blood allogeneic stem cell transplant. Whole blood will be collected and frozen prior to transplant. After documentation of CMV reactivation, defined as CMV at a level >/= 137 DNA copies/ml by PCR, autologous CMV-specific CTLs will be generated to be infused within 72 hours of CMV reactivation, if the patient has ANC engraftment, no acute GVHD or steroid administration </= 0.5 mg/kg dose. All outcomes will be recorded starting from the time of T-cell administration. While the dose of T-cells will vary depending on how many cells can be grown by ex vivo expansion after thawing and prior to administration, the maximum dose will be 10e5 viable CD3+ T cells/kg. It is anticipated that 20-25 patients per year will be accrued and that approximately 2 patients per month will develop CMV reactivation and thus be eligible to receive autologous CTLs. A maximum of 36 patients will receive autologous CTLs. The two primary endpoints, starting at the time of autologous T-cell administration, will be T = time to non-relapse mortality and Y = [28-day success], where "success" is defined as follows. CMV will be evaluated weekly at 7, 14, 21 and 28 days using PCR. Treatment will be considered a success if the patient does not require initiation of CMV anti-viral therapy. Anti-viral therapy will be started if 1) End-organ disease is documented at any time point after CTL administration 2) Increase in CMV DNAemia >50% compared with baseline at any time point 3) Decrease in CMV DNAemia <50% compared with baseline at day 21 after CTL administration and 4) CMV DNAemia >5000 copies/ml at any time point.

Non-relapse mortality is defined as death because of causes other than relapse of the underlying hematological malignancy. Relapse of underlying hematological malignancy will be a competing event for non-relapse mortality. Time to non-relapse mortality is defined as time to non-relapse mortality from date

of stem cell transplantation.

The Department of Biostatistics Clinical Trial Conduct (CTC) website will be used to monitor the time to non-relapse mortality, and the trial conduct will be implemented by a Statistical Analyst from the Biostatistics Department.

The Clinical Trial Conduct website is an MD Anderson portal for multi-center trials that provides treatment assignment, randomization, and monitoring for several hundred trials. The website was developed and is maintained by software developers in the Biostatistics department. There are approximately 7 different randomization algorithms implemented at the site, covering methods from simple randomization to innovative adaptive randomization. The trials and statistical details are overseen by the statisticians in the MD Anderson Biostatistics department. Users of the website (nurses, clinicians, etc) are registered on specific trials at the site and may be granted various levels of access (read only, write, blinded, etc).

BMTWeb is departmental clinical research application used to collect patient treatment data for patient receiving transplant in SCTCT department. It operates as a data repository for the clinical data transmitted to CIBMTR to meet our patient follow up requirements.

Sample Size. The effective sample size for evaluating CTL effects is the number of patients who suffer CMV reactivation, are eligible to receive CTLs, and actually receive CTLs, not the number enrolled and undergoing a transplant. In order to obtain a maximum of 36 patients who are treated with CTLs, assuming an accrual rate of 5 patients per month who receive a transplant and a 40% rate of patients with CMV who satisfy the entry criteria for receiving CTLs, it is expected that an effective accrual rate total of 2 patients per month will be enrolled, receive a transplant, and subsequently develop CMV. Due to the randomness of the treatable CMV subsample size, which is binomial in q = .40 and n = number of patients initially enrolled and transplanted, up to 105 patients will be enrolled (21 months accrual) to ensure at least a 90% probability that there will be at least 36 patients with CMV. If q = .50, then up to 83 patients (17 months accrual) will be enrolled to ensure this same sample size with this reliability. The overall sample size of 36 will ensure that, if the trial is not stopped early and, for example, 18/36 patients achieve 28-day success, then a posterior 95% credible interval for p starting with a beta (.50,.50) prior would be .342 - .658, or approximately 34% to 66%.

The first three patients on protocol will be observed for at least 28 days for safety monitoring before more patients are enrolled in the study.

Statistical Models and Early Stopping Rules

Probability of 28-day Success. The Bayesian method of Thall and Sung will be used to monitor the p = the probability of 28-day success. Assume that the number of 28-day successes Y ~ binomial(p, 36) and that *a priori* p ~ beta(.5, .5). The trial will be stopped early if Pr(p > .50 | data) < 0.010. Assuming a beta(500,500) prior for the standard response probability, and monitoring continuously, the trial will be stopped early if [# patients with 28-day success] / [# patients evaluated for 28-day success] is less than or equal to 0/5, 1/9, 2/12, 3/15, 4/18, 5/21, 6/24, 7/26, 8/29, 9/31, or 10/34.

Treatment Failure Event. Treatment failure event is defined as death, graft failure, or grade 3-4 toxicity secondary to CTL infusion in 6 months after CTL infusion. The Bayesian method of Thall, et al. will be used to monitor non-relapse mortality (regimen-related death, RRD). Assume that T ~ exponential with median m, and that *a priori* m ~ inverse gamma(3, 13.9), which has mean 6.96, corresponding to historical probability Pr(T < 6 months) = 0.45. The trial will be stopped early if Pr(m > 6.96 months | data) < 0.0717. In terms of median of T, the early stopping event is [m > 6.96 months], which is equivalent to [mean(T) > 10.04 months] because T follows an exponential distribution.

Early Deaths. If a patient treated for CMV dies from any cause before day 28, or drops out for some reason, that will be counted as a failure when scoring 28-day success. Due the lack of computer software to jointly model the two different types of death, regimen-related and not regimen-related, which are competing risks, and non-fatal 28-day failure, and implement a design which separates these events, if a death within 28-days is regimen-related, then the design will "double count" the event. Specifically, such a death will be scored as an event in the monitoring rule for m and also as a 28-day failure in the monitoring rule for p. Consequently, the monitoring rules are conservative. It is anticipated, however, that the actual probability of such very early deaths will be very small, so these considerations will not substantively affect trial conduct.

Operating Characteristics. The design's operating characteristics, with these two early stopping rules both implemented, are given below in Table 7. Due to the lack of computer software to evaluate the two monitoring rules together, (i) it is not possible to obtain achieved sample size distributions, and moreover (ii) it was necessary to compute the overall early stopping probability, given in the last column of Table 1, under the simplifying assumption that p and m are independent parameters, which if course is not true. However, denoting Sp = [stop due to the rule for p] and Sm = [stop due to the rule for m], since $Pr(Sp) = Pr(Sp \mid Sm)Pr(Sm) + Pr(Sp \mid \text{not } Sm)\{1 - Pr(Sm)\}$, if p and m are positively associated, which seems a reasonable assumption, then $Pr(Sp \mid Sm) > Pr(Sp)$ and $Pr(Sp \mid \text{not } Sm) < Pr(Sp)$, so it is unclear precisely how actual association between the two parameters will affect the joint behavior of the two rules. If appropriate computer software were available, this issue could be explored more precisely.

Secondary Outcomes. Additional outcomes will include overall survival time, disease-free survival time, relapse rate, secondary graft failure, and graft-versus-host disease as an ordinal outcome. Each of these variables which will be analyzed as a function of patient covariates using standard statistical methods, including Bayesian survival regression analysis and ordinal regression. Unadjusted event time distributions will be estimated using the Kaplan-Meier method.

Table 7. Operating characteristics of the two early stopping rules.

Scenario	P(Response)	P(Death < 6 Months)	P(Stop Early due to Response Rule)	P(Stop Early due to Death Rule)	P(Stop Early: Overall)
1	0.50	0.45	0.070	0.100	0.163
2	0.30	0.45	0.681	0.100	0.712
3	0.50	0.60	0.070	0.374	0.418
4	0.30	0.60	0.681	0.374	0.800
5	0.50	0.65	0.070	0.648	0.672
6	0.30	0.65	0.681	0.648	0.888

Stopping Rules

The Bayesian decision cut-off for the treatment failure time event is to **STOP** accrual to the trial if Prob(median > 6.96 | data) < 0.0717.

The following examples illustrate how this rule behaves with actual data. The key points in understanding the rule are that (1) each patent's data consist of either the time of the failure event if it occurred, or the patient's current following time if the event has not occurred and (2) all of the information needed by the rule is summarized by two statistics:
Nevents = the total number of events that have occurred
TFU = total follow up time

In general,
1) for given Nevents, larger TFU gives a smaller Prob(median > 6.96 | data)
2) for given TFU, larger Nevents gives a smaller Prob(median > 6.96 | data)

Example 1.
patient 1: event at 20 days
patient 2: followed for 100 days, no event
patient 3: event at 25 days
patient 4: event at 25 days

Nevents = 3, TFU = 170 ➔ Prob(median > 6.96 | data) = 0.066
Since this is smaller than the fixed decision cut-off .0717, the decision is **STOP**.

Example 2.
patient 1: event at 30 days
patient 2: followed for 100 days, no event
patient 3: event at 50 days
patient 4: event at 40 days

Nevents = 3, TFU = 220 ➔ Prob(median > 6.96 | data) = 0.089
Since this is larger than the fixed decision cut-off .0717, the decision is DO NOT **STOP**.

Example 3.
patient 1: event at 20 days
patient 2: followed for 100 days, no event
patient 3: followed for 70 days, no event
patient 4: event at 40 days
patient 5: event at 15 days
patient 6: followed for 40 days, no event
patient 7: event at 20 days

Nevents = 4, TFU = 305 ➔ Prob(median > 6.96 | data) = 0.062
Since this is smaller than the fixed decision cut-off .0717, the decision is **STOP**.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:

This study is not randomized nor blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

This study will be continuously monitored per the statistical design.

Protocol Monitoring Plan:

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MD Anderson
IND Number: 16063

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Moon Shots Program
Will your protocol be funded by the Moon Shots Program? Yes

Specific Disease Site(s): Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

Platform(s): Applied Cellular Therapy (ACT)

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Miltenyi Biotec
Support Type: Other: Miltenyi Biotec will cover the costs of manufacturing the CTLs.

This Sponsor/Supporter/Granting Agency will receive data.

Sponsor Name: Moon Shots Program
Support Type: Other: Moon Shots Program: ACT platform for AML/MDS

This Sponsor/Supporter/Granting Agency will receive data.

Regulatory Requirements

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Click here for help	No

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study involve human/animal tissue other than blood derived hematopoietic stem cells?	No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

- ○ Yes
- ● No
- ○ Not Applicable For This Protocol

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study?	Yes

Please provide the name of the responsible party, the facility or department, contact information and the name of the product or intermediate.
Manufacture of recipient derived autologous CMV specific CTLs under GMP conditions will be performed at the MD Anderson GMP facility using the CliniMACs device from Miltenyi Biotec.

Will you obtain an unlicensed (not FDA approved for use in humans) drug or biological product precursor or intermediate for use in patients?	No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree? No