BMT CTN 0802

A Multi-Center, Randomized, Double Blind, Phase III Trial Evaluating Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as Initial Systemic Treatment of Acute GVHD

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BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

A Multi-Center, Randomized, Double Blind, Phase III Trial Evaluating Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as Initial Systemic Treatment of Acute GVHD

BMT CTN PROTOCOL 0802
Version 3.0

Study Chair
Javier Bolaños-Meade, MD[1]

Study co-Chair
Vincent T. Ho, MD[2]

Protocol Team

Amin Alousi, MD[3]	Margaret MacMillan, MD[7]
Joseph Antin, MD[2]	Paul Martin, MD[8]
Kate Barowski[4]	Marco Mielcarek, MD[8]
Shelly Carter, ScD[4]	Brent Logan, PhD[6]
James Ferrara, MD[5]	Georgia Vogelsang, MD[1]
Mary Horowitz, MD[6]	Daniel Weisdorf, MD[7]
John Levine, MD[5]	

[1] Johns Hopkins University
[2] Dana Farber Cancer Institute
[3] University of Texas, MD Anderson Cancer Center
[4] The EMMES Corporation
[5] University of Michigan
[6] Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin
[7] University of Minnesota
[8] Fred Hutchinson Cancer Research Center

Core Study Participants:

Case Western Reserve University Consortium
  - Ohio State University
  - Oregon Health & Science University
  - University Hospitals of Cleveland
  - Washington University, Barnes Jewish Hospital
City of Hope National Medical Center
Dana Farber Cancer Institute
  - Brigham & Women's Hospital
  - Massachusetts General Hospital
Duke University Medical Center
Fred Hutchinson Cancer Research Center
Johns Hopkins
Memorial Sloan-Kettering Cancer Center
Pediatric Bone and Marrow Transplant
  - Children's Healthcare of Atlanta
  - Children's Medical Center of Dallas
  - Children's Memorial - Northwestern
  - Hackensack University Medical Center
  - Levine Children's Hospital
  - Medical University of South Carolina
  - Nationwide Children's Hospital
  - OHSU, Doernbecher Children's Hospital
  - Penn State College of Medicine
  - Roswell Park Cancer Institute, Pediatric BMT
  - UCLA, Mattel Children's Hospital
  - University of Alabama at Birmingham
  - University of Mississippi Medical Center
  - University of North Carolina at Chapel Hill
  - University of Utah/ Primary Children's Medical
    Center
Stanford Hospital and Clinics
University of California, San Diego Medical Center
University of Florida College of Medicine
University of Michigan Cancer Center
University of Minnesota
University of Pennsylvania
University of Texas, MD Anderson Cancer Center

Affiliate Study Participants:

Avera Hematology & Transplant Center
Banner Research Institute
Baylor University Medical Center
Beth Israel Deaconess Medical Center
Blood & Marrow Transplant Program at
   Northside Hospital
Colorado Blood Cancer Institute
Hackensack University Medical Center
Indiana BMT at Beech Grove
Loyola University Medical Center
Mayo Clinic
Medical College of Wisconsin
Rush University Medical Center
Texas Transplant Institute
Tufts Medical Center
University of Iowa Hospital & Clinics
Utah BMT/ University of Utah Medical
   School
Virginia Commonwealth University,
   MCV Hospital
Weill Cornell Medical College

PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0802

A Multi-Center, Randomized, Double Blind, Phase III Trial Evaluating Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as Initial Systemic Treatment of Acute GVHD

Principal Investigator: Javier Bolaños Meade, MD
Co-Principal Investigator: Vincent T. Ho, MD

Study Design:

The study is a Phase III, randomized double blind, placebo controlled trial evaluating the addition of MMF vs. placebo to systemic corticosteroids as initial therapy for acute GVHD. The primary endpoint will be GVHD free survival at Day 56 post randomization.

Corticosteroids have been used as primary therapy for acute GVHD for many years. Historical published and unpublished data from Johns Hopkins, M. D. Anderson, University of Michigan and others defined an expected 35%-53% complete response (CR) at Day +28 of corticosteroid therapy for previously untreated patients with acute GVHD.

BMT-CTN 0302 was a randomized Phase II study evaluating etanercept, mycophenolate mofetil, denileukin diftitox or pentostatin in addition to corticosteroids. The results of that study suggested that mycophenolate mofetil produced the highest rates of CR at Day 28 and overall survival, supporting its evaluation in a Phase III study. Day 56 GVHD-free survival for the four treatment arms (all combining corticosteroids with one of the four study drugs) ranged from 39-71% across the four study arms.

In this trial, patients with newly diagnosed acute GVHD will receive corticosteroids and will be randomized to also receive either placebo or mycophenolate mofetil. Each arm will be assessed for safety (stopping rules defined) and efficacy.

Primary Objective:

The primary objective is to estimate graft-versus-host disease free survival (acute or chronic) at Day 56 after randomization without additional therapy.

Secondary Objectives:

Secondary objectives include:
1. Proportions of complete, partial (PR), mixed response, no response and progression among surviving patients at Day 14, 28 and 56.
2. Treatment failure (treatment failure defined as: no response, progression, administration of additional therapy for GVHD, or mortality) at Day 14, 28, and 56.

3. The incidence of acute GVHD flare after CR/PR requiring additional agent (including 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) for systemic therapy before Day 56 post-randomization.
4. Incidence of discontinuation of immune suppression without acute GVHD flare and without disease progression/recurrence by Days 56, 180, and 360 post-therapy.
5. Steroid dose at Day 28 and 56 post-randomization.
6. Incidence of topical/non-absorbable therapy given by Day 56.
7. Incidence of chronic GVHD by 6 and 12 months post-randomization.
8. Overall and GVHD-free survival at 6 and 12 months post-randomization.
9. Incidence of systemic infections within 6 months of initiation of therapy.
10. Incidence of EBV-associated lymphoproliferative disorder or EBV reactivation requiring therapy.
11. Disease-free survival at 6 and 12 months post randomization.
12. Non-relapse mortality at 6 and 12 months.
13. Change in patient-reported outcomes from enrollment to Day 56.

Eligibility: Patients must have acute GVHD (grade I-IV) requiring systemic therapy. No previous systemic immune suppressive therapy for acute GVHD is allowed except for a maximum 72 hours of prior corticosteroid therapy. Patients receiving MMF within 7 days of screening will be excluded. Patients must have an absolute neutrophil count (ANC) greater than 500/µL. Patients with acute GVHD after salvage donor lymphocytes are not eligible (preplanned DLI is allowed).

Treatment Description: All patients will receive prednisone 2 mg/kg/day PO (or methylprednisolone at 1.6mg/kg/day IV) divided in 1-2 daily doses. Prednisone may be tapered as tolerated according to institutional practice. However, prednisone taper may not start sooner than 3 days after randomization, and the prednisone dose can not be less than 0.25 mg/kg/day prednisone (methylprednisolone 0.2 mg/kg/day) at Day 28 post-randomization.

Patients will be randomized in a 1:1 fashion to receive either placebo or mycophenolate mofetil 1 gm PO or IV every 8 hours. Study drug (MMF/Placebo) should be discontinued by Day 56, or when prednisone taper is complete, whichever occurs first.

Patients developing acute GVHD during GVHD prophylaxis (e.g. calcineurin inhibitor, sirolimus, etc.) should have their prophylaxis

medication continued during the study period if possible. Concurrent or addition of topical steroid therapy (skin creams, oral beclomethasone, and other non-absorbable steroids) is allowed.

In addition to prescribed study drug plus corticosteroids, all patients should receive transfusion support per institutional practice; anti-infective prophylaxis against herpes viruses, *Pneumocystis jiroveci,* bacterial and fungal infections should be followed according to institutional practices. Pre-emptive monitoring and treatment strategy for CMV is strongly recommended.

GVHD organ stage scores, overall clinical grade, biopsy information for GVHD, GVHD medications, presence of chronic GVHD, and steroid dose will be recorded weekly and reported to the BMT CTN Data Coordinating Center (DCC).

Accrual Objective: 186 patients will be accrued per study arm (a total of 372 patients).

Accrual Period: The estimated accrual period is 3 years.

Study Duration: Patients will be followed for 12 months following initiation of therapy.

STUDY SCHEMA

Aim: To determine if the addition of mycophenolate mofetil to corticosteroids as initial therapy for acute GVHD improves GVHD free survival and overall clinical outcome.

Inclusion Criteria	Exclusion Criteria
1. Acute GVHD diagnosed after allogeneic hematopoietic stem cell transplant using either bone marrow, PBSC or cord blood.	1. Mycophenolate mofetil or mycophenolic acid (Myfortic) given within 7 days of enrollment.
2. Acute GVHD developing after pre-planned DLI is eligible.	2. Active uncontrolled infection.
3. Grade I-IV acute GVHD requiring systemic therapy.	3. Relapsed/persistent malignancy requiring rapid immune suppression withdrawal.
4. Patients of all ages will be included.	4. Patients that have undergone an unscheduled (or not part of original transplant therapy plan) DLI.
5. Biopsy confirmation of GVHD is recommended, but not required. Enrollment should not be delayed awaiting biopsy or pathology results.	5. Patients unlikely to be available at the transplant center on Day 28 and 56 of therapy.
6. The patient must have received no previous systemic immune suppressive therapy for **treatment** of acute GVHD, except for a maximum 72 hours of prior corticosteroid therapy	6. A clinical syndrome resembling de novo chronic GVHD developing at any time after BMT.
	7. Other drugs for GVHD treatment
7. Clinical status at enrollment to allow tapering of prednisone to not less than 0.25 mg/kg/day prednisone (0.2 mg/kg/day methylprednisolone) at Day 28 of therapy	8. If any prior steroid therapy (for indication other than GVHD), treatment at doses > 0.5 mg/kg/day methyl-prednisolone within 7 days prior to onset of GVHD.
8. ANC greater than 500/µL.	9. Patients who are pregnant, breast feeding, or if sexually active, unwilling to use effective birth control for the duration of the study.
9. Signed informed consent and/or assent.	10. Adults unable to provide informed consent
10. Assent and educational materials provided to, and reviewed with, patients under the age of 18.	11. Patient on dialysis.
	12. Patients with severe veno-occlussive disease of the liver who in the judgment of the treating physician are not expected to have normalized bilirubin by Day 56.
	13. Patients with a history of intolerance/allergy to MMF.

After 3 days of full dose corticosteroids + MMF/placebo: Taper steroids as tolerated according to institutional practices, but to no less than 0.25 mg/kg/day prednisone (or 0.2 mg/kg/day methylprednisolone) on Day 28. Steroid taper may not start sooner than 3 days after randomization if GVHD is improving. Improvement is defined as any clinically recognizable lessening of skin rash, redness, or extent; lessening of diarrhea or lowered bilirubin (though it does not have to be greater than or equal to one stage improvement in any involved organ), without worsening in any organ.
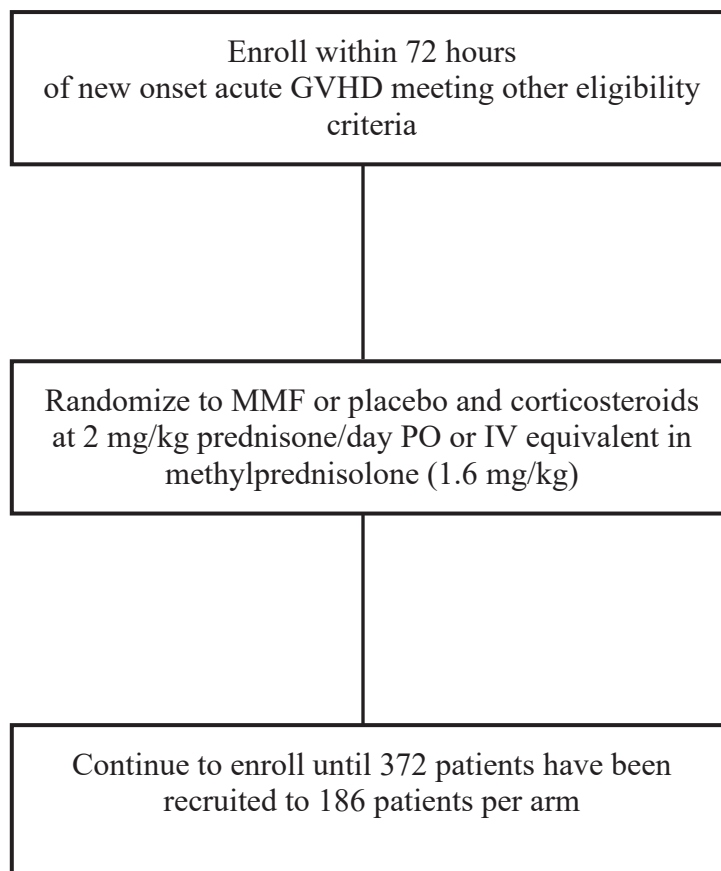
If acute GVHD progresses within 5 days or no response within 14 days, then treat with alternative systemic secondary GVHD therapy at the physician's discretion. This patient would be considered a failure for the primary endpoint. This patient will be considered "off study treatment", but will remain on study to be followed for study endpoints.

If acute GVHD flares during taper of prednisone, steroid dosing may be re-escalated or secondary therapy added at the discretion of the treating physician. Re-escalation of steroid for GVHD flare alone will not be considered as treatment failure.

STUDY SCHEMA (cont'd)

***Suggested* prednisone taper for responders (round to nearest 5 mg of prednisone):** 2 mg/kg/day once or twice a day Days 1-5. 1.5 mg/kg/day once daily Days 6-10. 1 mg/kg/day Days 11-15. 0.5 mg/kg/day Days 16-20 0.25 mg/kg/day Days 21-28 (prednisone may be tapered as tolerated to no less than 0.25 mg/kg/day (methylprednisolone 0.2 mg/kg/day) at Day 28. Then taper according to institutional guidelines. The goal is to get to ≤ 0.2 mg/per/kg per day of prednisone or ≤ 0.16 mg/per/kg per day of methylprednisolone by Day 56.	**Primary endpoint:** - Acute and chronic GVHD free survival at Day 56 after randomization. **Secondary endpoints:** - Proportion of CR, PR, mixed response, no response and progression, among surviving patients at Days 14, 28 and 56. - Treatment failure (defined as no response, progression, administration of additional therapy fro GVHD, or mortality) at Days 14, 28, and 56. - Incidence of acute GVHD flares after CR/PR requiring additional agents (including 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) for systemic therapy before Day 56. - Incidence of discontinuation of immune suppression without acute GVHD flare and without disease progression/recurrence by Days 56, 180, and 360 post-therapy. - Steroid dose at Day 28 and Day 56. - Incidence of topical/non absorbable therapy at Day 56. - Incidence of Chronic GVHD by 6 and 12 months. - Overall and GVHD free survival at 6 and 12 months after randomization. - Incidence of systemic infections within 6 months of therapy. - Incidence of EBV PTLD or EBV reactivation requiring therapy. - Disease-free survival at 6 and 12 months post randomization. - Non-relapse mortality at 6 and 12 months post randomization. - Change in patient-reported outcomes from enrollment to Day 56.

STUDY DESIGN SCHEMATIC

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┌─────────────────────────────────────────────┐
│             Enroll within 72 hours           │
│ of new onset acute GVHD meeting other        │
│            eligibility criteria              │
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│ Randomize to MMF or placebo and              │
│ corticosteroids at 2 mg/kg prednisone/day    │
│ PO or IV equivalent in methylprednisolone    │
│ (1.6 mg/kg)                                  │
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│ Continue to enroll until 372 patients have   │
│ been recruited to 186 patients per arm       │
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Primary Endpoint:
Proportion of patients surviving at Day 56 after enrollment without acute or chronic GVHD and without other systemic agents added for treatment of GVHD.

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CHAPTER 1

1.   BACKGROUND AND RATIONALE

1.1.   Acute Graft-vs.-Host Disease

Acute graft-versus-host disease (GVHD) is the major complication of allogeneic hematopoietic stem cell (HSC) transplantation.[1] Acute GVHD produces significant morbidity and complicates patient management, resulting in organ toxicity, frequent infections, malnutrition and substantial delay in recovery from transplantation.

Acute GVHD usually occurs within the first 3-4 months of allogeneic HSCT and may involve the skin, liver and intestinal tract. It is believed that T-lymphocytes contained in the donor graft respond in vivo to disparate major (HLA) or minor (non-HLA) histocompatibility antigens expressed by recipient tissues, initiating a cascade of events leading to the signs and symptoms of acute GVHD.[1]

The syndrome of acute GVHD includes the following signs and symptoms. Skin involvement (maculopapular exanthem) is usually the first sign. Lesions may be pruritic or painful, red to violaceous in color, and often involve the palms and soles. Acute GVHD of the gut may involve the stomach, small bowel and colon producing persistent nausea and vomiting or profuse diarrhea, intestinal bleeding, cramping abdominal pain and ileus. Liver GVHD produces cholestatic liver injury with hyperbilirubinemia and, in some cases, hepatocellular enzyme elevations.

The use of cyclosporine (CSA) or tacrolimus (FK) plus short course methotrexate (MTX) has lowered the risk for acute GVHD compared to single agent or other combination therapy, but even with these regimens, 35-50% of patients develop Grade 2-4 acute GVHD.[1, 2, 3] Older recipients or those with unrelated or partially HLA-matched donors may develop more frequent or possibly more therapy-resistant acute GVHD.

1.2.   Primary Therapy for Acute GVHD

Corticosteroids have served as the primary therapy for acute GVHD for over three decades. There is some variability among investigators and transplant centers regarding the optimal starting dose of corticosteroids, particularly in early stage GVHD. However, a recommended initial dose of corticosteroids for moderate to severe (Grade II-IV) acute GVHD accepted in most transplant centers is 2 mg/kg/day of methylprednisolone, or an equivalent steroid.[1, 2, 3] The response rate to single-agent corticosteroid therapy, when analyzed in large retrospective reviews is approximately 50%.[4, 5] Doses higher than 2 mg/kg/day have not been associated with improvement in response rates.[6] Despite an initial response, many patients will experience a flare of their GVHD upon steroid taper, and the durability of response is often substantially lower. In acute GVHD developing after matched unrelated and related donor transplantation, durable remission of acute GVHD with steroid alone were reported in only 24% and 40% of patients, respectively.[7, 8]

Response to initial treatment is a key predictor of clinical outcome. Mortality in patients with grade II-IV acute GVHD is greatest among those who fail to achieve a complete response to initial treatment.[4, 5, 8, 9] A very early response, as evidenced by the ability to begin a steroid taper on Day 5 of therapy is also associated with a favorable prognosis.[10] It is possible that early responders do better, at least in part, because the steroid taper begins sooner and reduces the risk of complicating opportunistic infections, a common cause of death. In general, cutaneous disease responds promptly but lower gastro-intestinal and hepatic involvement responds less well to therapy.[4] Other risks for failure of initial therapy include early onset of GVHD, increasing HLA disparity and older age.[4, 5]

The suboptimal response and long-term survival associated with corticosteroids alone has prompted investigation of additional immunosuppressive agents in the initial therapy of acute GVHD. Unfortunately, this strategy has to date not yielded superior outcomes compared to steroids alone. In some cases, the benefit of better initial GVHD control with an additional agent is offset by a higher risk of infection or other side effects. The most widely studied agent in this context is anti-thymocyte globulin (ATG). Single arm Phase II studies of prednisone + ATG as initial therapy of acute GVHD have reported response rates from 67% to 80%.[11, 12] However, in a randomized trial of prednisolone ± equine ATG, there was no difference in response rates or survival, but infectious morbidity, especially CMV disease and pneumonitis, was higher in the combined immunosuppression group.[13]

Other biologic agents have also been studied as an adjunct to corticosteroids as initial therapy for acute GVHD. Lee et al randomized 102 patients to receive the monoclonal anti-CD25 (the IL-2 receptor alpha chain) antibody, daclizumab (1 mg/kg) on Days 1, 4 and weekly thereafter or placebo in conjunction with corticosteroids. While response rates were similar in both groups (53 vs. 51%), survival at 100 days and 1 year was inferior in the steroid + daclizumab group.[14] A randomized study evaluating BT563 (an antibody against the IL-2 receptor) also did not demonstrate an advantage over placebo when combined with prednisone alone.[15] A randomized trial adding a CD5-specific immunotoxin vs placebo to methylprednisolone also yielded similar clinical results.[16] Manifestations of acute GVHD responded more quickly in the immunoconjugate arm, but benefits were not durable. Finally, Uberti et al reported a 75% response rate in 20 patients with biopsy proven acute GVHD when etanercept, a recombinant TNF-alpha receptor fusion protein capable of neutralizing TNF, was given in conjunction with corticosteroids with tacrolimus.[17]

Recently, the Blood and Marrow Transplant Clinical Trials Network completed a multi-center randomized, four-arm, Phase II trial (BMT CTN 0302) designed to identify the most promising agent for combination with steroids as initial therapy for the treatment of GVHD.[18] Between August 2005 and March 2008, 180 patients with newly diagnosed GVHD were randomized to receive steroids (2 mg/kg/day methylprednisolone) plus either etanercept, mycophenolate mofetil, denileukin diftitox or pentostatin. The primary objective was to estimate the complete response rate at Day 28 for each of the four agents and evaluate secondary outcomes pertinent to the best agent for testing in a planned follow-up Phase III trial against steroids alone. The median age of patients was 50 yrs (range, 7.5–69.9) with 96% >18 yrs; 39% had AML and 63% were male. The graft was peripheral blood (PB) in 61%, bone marrow (BM) in 25% and cord

blood (CB) in 14%. Myeloablative conditioning was used for 66% of patients, and 53% of patients had unrelated donors. Forty-four patients (24%) received mycophenolate mofetil as GVHD prophylaxis and were randomized to 1 of the 3 non-mycophenolate mofetil arms.

At enrollment, 68% of patients had grade I-II GVHD; 32% had grade III/IV GVHD. Fifty-three percent of patients had visceral organ involvement at the time of enrollment. The treatment arms were balanced except cord blood grafts were more common in the denileukin diftitox arm (26%, p=0.006); peripheral blood grafts were more common in the etanercept arm (78%, p=0.006); and the mycophenolate mofetil arm had more myeloablative transplants (82%, p=0.04). The proportion of complete responses at Day 28 were: etanercept (26%), mycophenolate mofetil (60%), denileukin diftitox (53%) and pentostatin (38%). Day 56 complete plus partial response rates were 59%, 78%, 68%, and 71%, respectively. Six month chronic GVHD (cGVHD) incidence was: etanercept (21%), mycophenolate mofetil (25%), denileukin diftititox (29%), and pentostatin (24%). Overall survival at 6 months was etanercept (59%), mycophenolate mofetil (71%), denileukin diftitox (63%), and pentostatin (55%), respectively. After excluding patients who received mycophenolate mofetil prophylaxis, the mycophenolate mofetil arm still had the highest Day 28 complete response rate and overall survival. Overall toxicities and post-randomization infections were less frequent in patients randomized to mycophenolate mofetil and etanercept. These efficacy and toxicity data, particularly response, survival, cGVHD, and infections, suggest that mycophenolate mofetil in conjunction with steroids to be the most promising regimen to compare against steroids alone in a randomized Phase III trial. A summary of the results can be seen in Table 1.2. With these data in mind, we have developed the current Phase III study to further test the addition of mycophenolate mofetil to steroids as initial therapy of GVHD.

TABLE 1.2: SUMMARY OF STUDY RESULTS FOR BMT CTN 0302

Outcome	Treatment Arm							
	Etanercept (N=46)		MMF (N=45)		Denileukin Diftitox (N=47)		Pentostatin (N=42)	
Day 28 CR	12 (26%)	Skin: 12/36 (33%)	27 (60%)	Skin: 21/35 (60%)	25 (53%)	Skin: 17/35 (49%)	16 (38%)	Skin: 14/34 (41%)
		L.G.I.: 4/12 (33%)		L.G.I.: 12/18 (67%)		L.G.I.: 5/14 (36%)		L.G.I.: 7/17 (41%)
		U.G.I.: 5/10 (50%)		U.G.I.: 11/12 (92%)		U.G.I.:10/14 (71%)		U.G.I.: 8/13 (62%)
		Liver: 2/6 (33%)		Liver: 5/7 (71%)		Liver: 3/7 (43%)		Liver: 2/5 (40%)
Day 28 CR (excl. prior MMF)	9 (28%)		27 (60%)		15 (48%)		11 (39%)	
Day 28 CR/PR	22 (48%)		35 (78%)		28 (60%)		26 (62%)	
Day 56 CR/PR	27 (59%)		35 (78%)		32 (68%)		30 (71%)	
Day 56 Trea tment Fail	12 (26%)		4 (9%)		12 (26%)		13 (31%)	
OS Post-Randomization at 6 months	59% (95% CI: 43%- 72%)		71% (95% CI: 54%- 82%)		63% (95% CI: 47%- 76%)		55% (95% CI: 38%- 69%)	
OS Post-Randomization at 6 months (excl. prior MMF)	70% (95% CI: 51%-83%)		71% (95% CI: 54%-82%)		61% (95% CI: 40%-76%)		54% (95% CI: 33%-71%)	
Cum Incidence of Initial D/C of steroids at 9 months	34% (95 % CI: 20%- 48%)		31% (95% CI: 17%-45%)		20% (95% CI: 8%-32%)		20% (95% CI: 8%-33%)	
Cum Incidence Day 56 Grade 3-5 Toxicity (%)	76% (95% CI: 63%-88%)		80% (95% CI: 67%-92%)		76% (95% CI: 64%-89%)		67% (95% CI: 52%-81%)	
Cum Incidence Severe/ Life Threatening/ Fatal Infections at Day 270	47% (95% CI: 32%-62%)		44% (95% CI: 29%-59%)		58% (95% CI: 43%-72%)		56% (95% CI: 40%-71%)	
Cum Incidence of acute GVHD Flare after CR at Day 90	36% (95% CI: 21%- 50%)		28% (95% CI: 14%- 41%)		35% (95% CI: 21%- 49%)		36% (95% CI: 21%- 51%)	
Cum Incidence of cGVHD at Day 180	21% (95% CI: 9%- 33%)		25% (95% CI: 11%- 39%)		29% (95% CI: 15%- 43%)		24% (95% CI: 10%- 38%)	
Cum Incidence of Relapse at Day 180	14% (95% CI: 3%- 24%)		10% (95% CI: 1%- 19%)		9% (95% CI: 1%- 19%)		13% (95% CI: 2%- 24%)	

1.2.1. Mycophenolate Mofetil/Placebo

Pharmacology and Mechanism of Action
Mycophenolate mofetil (MMF) is a morpholinoethyl ester of mycophenolic acid (MPA). A product of several penicillium species, MPA possesses antibacterial, antifungal, antiviral, antitumor and immunosuppressive properties. MMF is a pro-drug since the immunosuppressive activity is evident only after hydrolysis to MPA. MMF was developed to enhance the bioavailability of MPA. MPA mediates its effect by inhibiting inosine monophosphate dehydrogenase (IMPDH), an enzyme that catalyzes the oxidation of inosine monophosphate to xanthine monophosphate, an intermediate metabolite in the synthesis of guanosine triphosphate (GTP). Lymphocytes rely on the de novo purine synthesis pathway for the nucleotides necessary for DNA synthesis; other cells can also rely on the salvage pathway. The action of MPA results in the depletion of the nucleotide pool in cell synthesis. An additional mode of action of MPA may be that, by depletion of GTP, it inhibits recruitment of leukocytes to sites of inflammation by inhibiting the glycosylation of lymphocyte glycoproteins involved in intercellular adhesion.

MMF in acute GVHD
Mycophenolate mofetil (MMF) is an agent already commonly used as GVHD prophylaxis, or treatment of steroid refractory GVHD after allogeneic SCT. MMF suppresses T cell proliferation by reversibly inhibiting the synthesis of the purine guanosine triphosphate. Basara *et al* initially reported a 65% response rate in 17 patients with steroid-refractory acute GVHD and updated the series to include 36 patients.[19, 20] Similar response rates were noted in other small studies.[21, 22] MMF is also used commonly in combination with a calcineurin inhibitor as a GVHD prophylaxis regimen for allogeneic SCT, especially in reduced intensity conditioning transplantation and umbilical cord blood transplantation.[23, 24, 25]

Pharmacokinetics of MMF and GVHD responses
Pharmacokinetic studies in solid organ transplantation suggest that MMF therapeutic efficacy may be improved when MMF is administered as q8hrs dosing instead of q12 hours dosing.[26, 27] Furthermore, there is extensive experience with using MMF at TID dosing in the GVHD prophylaxis setting after allogeneic SCT, and this higher dosing schedule has been to be well tolerated. Pharmacokinetic studies from the antecedent phase II trial (BMT CTN 0302), where the starting MMF dose was 1 gram BID, have further shown that an increase in MMF dosing to q8Hrs (TID) may be warranted, as described below.

Among the 180 subjects enrolled in the BMT CTN 0302 Acute GVHD Trial from November 2005 to March 2008, 45 subjects were randomized to MMF. Blood samples for pharmacokinetic analyses of mycophenolic acid (MPA, the active metabolite of MMF) were available for 32 of the 45 subjects in the first 2 weeks of treatment. Although the sample size was small, PK data from these patients showed that following dosing at 1 gm BID, 45-59% of the trough levels were low (defined as MPA trough <0.5 mcg/mL, or free MPA troughs <15 ng/mL), while < 5% had levels that were considered high. These results confirm that a sizeable fraction of patients likely had under-dosing of MMF on the 1gm BID schedule. Analysis of MPA levels with GVHD responses in this trial further demonstrated that trough MPA concentrations affect efficacy. Although MPA within the first 2 weeks of treatment did not appear to influence response at Day

28, MPA total (>0.5 mcg/mL) and free (>15 ng/mL) troughs were associated with higher CR/PR at Day 56.

Based in part upon these results, the starting dose of MMF/placebo in the current proposed trial will be 1gm TID. We believe that this schedule will insure that a greater proportion of patients will have therapeutically suitable drug exposure. Treating physicians will be given discretion for reducing the MMF/Placebo dose from TID to BID base on potential toxicities (Section 2.5), and the rates of sustained dose reductions on both arms will be monitored in interim analyses to assure patient safety (see monitoring plan, Section 4.25 and Chapter 5).

CHAPTER 2

2.   STUDY DESIGN

2.1.   Study Design

This trial is designed to evaluate the best therapy for acute GVHD in a prospective, multi-center, randomized, double blind Phase III trial. Each study arm will include corticosteroids plus either mycophenolate mofetil or placebo.

Accrual Objective:	186 patients will be accrued per study arm (a total of 372 patients).
Accrual Period:	The estimated accrual period is 3 years.
Study Duration:	Patients will be followed for 12 months following initiation of therapy.

2.2.   Primary Objective and Rationale for Study Design

The primary objective is to estimate graft-versus-host disease free survival (acute or chronic) at Day 56 after randomization to steroids plus mycophenolate mofetil or steroids plus placebo without additional therapy. Data from BMT CTN 0302 identified mycophenolate mofetil as the most promising agent to be tested in this Phase III study and was the most effective and least toxic of the drugs tested (mycophenolate mofetil, etanercept, pentostatin and denileukin diftitox).

2.3.   Eligibility

2.3.1.   Inclusion Criteria

Biopsy of involved tissue is strongly encouraged, but not required for study entry. The clinical diagnosis of acute GVHD requiring systemic therapy with corticosteroids is necessary for enrollment on the trial. Enrollment and randomization includes commitment to continue both steroids and study drug as indicated by the protocol as well as the required follow-up observations. If the intention to treat a patient depends on histologic results, the patient should not be enrolled on the BMT CTN 0802 study until the results are known. Patients can be enrolled only with a clinically established diagnosis. Histologic confirmation of acute GVHD is not required, but can be used as supportive evidence for the diagnosis. If an unexpected biopsy result occurs, and the treating physician feels it is necessary to take the patient off study, the center should contact the protocol chair.

1. Acute GVHD developing after allogeneic hematopoietic stem cell transplant using either bone marrow, peripheral blood stem cells or cord blood. Recipients of non-myeloablative and myeloablative transplants are eligible.

2. Acute GVHD after planned donor lymphocyte infusion or planned T cell addback are eligible.

3. De novo acute GVHD requiring systemic therapy. GVHD is defined as the presence of skin rash and/or persistent nausea, vomiting, and/or diarrhea and/or cholestasis presenting in a context in which acute GVHD is likely to occur and where other etiologies such as drug rash, enteric infection, or hepatotoxic syndromes are unlikely or have been ruled out. Note that patients with stage I and II skin only (overall grade I) or isolated upper gastrointestinal (GI) involvement are eligible if the treating physician deems that systemic high-dose corticosteroid treatment is indicated.

4. The patient must have had no previous systemic immune suppressive therapy for treatment of acute GVHD except for a maximum 72 hours of prior corticosteroid therapy at >0.5mg/kg/day methylprednisolone or equivalent <u>after</u> the onset of acute GVHD.

5. Clinical status at enrollment to allow tapering of steroids to not less than 0.25 mg/kg/day prednisone (0.2 mg/kg/day methylprednisolone) at Day 28 of therapy.

6. Absolute neutrophil count (ANC) greater than 500/μL.

7. Written informed consent and/or assent from patient, parent or guardian.

8. Documentation that the assent document and education materials have been provided to, and reviewed with, patients between the ages of 7 and 17.

9. Patients of all ages are eligible.

10. Biopsy confirmation of GVHD is recommended, but not required. Enrollment should not be delayed for biopsy or pathology results unless these are to be used to decide about whether to treat for GVHD.

2.3.2. Exclusion Criteria

1. Patients receiving mycophenolate mofetil or mycophenolic acid (Myfortic) within seven days of screening for enrollment.

2. Patients with uncontrolled infections will be excluded. If a bacterial or viral infection is present, patients must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to enrollment. If a fungal infection is present, patients must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to enrollment.

   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.

3. Relapsed/persistent malignancy requiring rapid immune suppression withdrawal.

4. Patients with GVHD after an unplanned DLI, i.e., DLI that was not part of their original transplant therapy plan, or DLI given for treatment of persistent or recurrent malignancy after transplantation.

5. Patients unlikely to be available at the transplantation center on Day 28 and 56 of therapy.

6. A clinical syndrome resembling de novo chronic GVHD developing at any time after allotransplantation.

7. Patients receiving other drugs for the treatment of GVHD.

8. Patients receiving methylprednisolone > 0.5 mg/kg/day (or 0.6 mg/kg/day prednisone) within 7 days <u>before</u> the onset of acute GVHD. If steroid therapy has been administered for treatment of a non-GVHD related condition and tapered to ≤ 0.5 mg/kg/day methylprednisolone (0.6 mg/kg/day prednisone) for seven or more days before the onset of acute GVHD, the patient is eligible.

9. Patients who are pregnant, breast feeding, or, if sexually active, unwilling to use effective birth control for the duration of the study. Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding, therefore breast feeding patients are not eligible.

10. Adults unable to provide informed consent.

11. Patients on dialysis.

12. Patients with severe hepatic VOD or sinusoidal obstruction syndrome who in the judgment of the treating physician are not expected to have normalized bilirubin by Day 56 after enrollment.

13. Patients with a history of intolerance/allergy to MMF.

2.3.3. Informed Consent

The informed consent process will begin at recognition of subject eligibility and consent will be obtained per institutional practices before study therapy is initiated.

2.4. Treatment Plan

2.4.1. Randomization

After registration and enrollment, the study participant will be randomized in a 1:1 fashion to receive either MMF or placebo as described in Chapter 5.

2.4.2. Corticosteroid Dosing and Taper

All patients enrolled on this trial will receive steroids at a dose of prednisone 2mg/kg/day PO (or methylprednisolone 1.6 mg/kg/day IV) as therapy of acute GVHD. Pediatric patients unable to take tablets can use oral prednisolone solution 2 mg/kg/day. Steroid taper may follow local institutional practice. However, for those improving, ***steroid taper may not start sooner than 3 days after randomization and the steroid dose must not be tapered to less than 0.25 mg/kg/day prednisone (or 0.2 mg/kg/day methylprednisolone) on Day 28***.

The following is a *suggested* prednisone taper.

Suggested taper for responders
(2 mg/kg/day prednisone orally=1.6 methylprednisolone mg/kg/day I.V.)

> 2 mg/kg/day of prednisone orally (or 1.6 mg/kg/day of methylprednisolone I.V) divided once or twice/day Days 1-5
>
> 1.5 mg/kg/day once daily Days 6-10
>
> 1 mg/kg/day once daily Days 11-15
>
> 0.5 mg/kg/day of prednisone once daily Days 16-20
>
> 0.25 mg/kg/day of prednisone once daily Days 21-28
>
> Patients should be tapered as tolerated to no less than 0.25 mg/kg/day (methylprednisolone 0.2 mg/kg/day) by Day 28.
>
> Then taper according to institutional guidelines with a goal to reach $\leq$ 0.2 mg/per/kg per day of prednisone or $\leq$ 0.16 mg/per/kg per day of methylprednisolone by Day 56.

2.4.3.   MMF/Placebo Formulation, Dosing, and Duration

Study treatment (MMF/placebo) should be initiated as soon as possible after randomization. A maximum of 48 hours is allowable.

Formulation and Drug Supply

MMF/Placebo will be obtained by the BMT CTN/EMMES, and distributed through an independent contractor. Questions regarding study drug orders and study drug distribution should be directed to the trial protocol coordinator at EMMES. MMF/placebo will be provided by the BMT CTN for up to 8 weeks. Oral MMF/placebo is available as 250 mg capsules in bottles of 70 each. Capsules should be stored at room temperature.

Intravenous: MMF/placebo for intravenous use will be supplied as a lyophilized powder. The study drug will be reconstituted by injecting 5% Dextrose in Water (D5W) into each vial. Intravenous MMF/placebo does not contain an antibacterial preservative; therefore, the study drug should be prepared under aseptic conditions. Reconstitute each vial with 14 mL D5W. Gently shake vial to dissolve the drug. Further dilute into D5W for a final concentration of 6 mg/mL. Dilute 1-g doses in 140 mL D5W. Intravenous mycophenolate is incompatible with normal saline and other saline containing diluents. Only D5W solution should be used for reconstitution and infusion solution. Infusion lines should be flushed only with D5W.

The Pharmacist at each center should prepare each dose of drug to avoid errors. Because of the potential teratogenic effects of MMF, pharmacists should follow institutional guidelines for the preparation of similar types of solutions. At the completion of the study, unused MMF/Placebo study drug should be returned to the study team by the patient for destruction as per institutional practice of the Investigational Pharmacy.

The investigator (and/or hospital pharmacist) will ensure that all study drug is stored in a secured area under recommended storage conditions and is dispensed by qualified staff members. All study drug will be accounted for on medication inventory sheets.

The BMT CTN will be allowed at intervals, and upon request during the study, to check unused supplies. Accounting for the use of supplies will be by reference to each center's record of supplies received, the dispensing records for the total number of patients enrolled at each center and the unused and returned supplies.

The investigator is responsible for maintaining drug accountability records. Drug accountability records will be reviewed during monitoring visits. Each institution may use their own drug accountability log. Study drug must be administered only to patients enrolled in this study as per the protocol.

Dose and Administration

For BMT CTN 0802, the dose of MMF will be different than the one used in 0302. This is based on the pharmacologic analysis of patients receiving MMF enrolled on BMT CTN 0302. This will insure a substantially greater proportion of patients will have therapeutically suitable drug exposure.

Oral dosing should be delivered in either 250 mg units or identical blinded placebo.
For those < 40 kg, IV dosing should be within ± 10% of the exact dose. Intravenous doses are infused over a two-hour period. The study drug capsule may not be opened to administer.

- Patients who weigh > 60 kg should receive MMF 1 gm PO/IV every 8 hours.

- Patients who weigh between 40-60 kg should receive 750 mg PO/IV every 8 hours.

- Patients who weigh <40 kg should receive 20 mg/kg IV or PO (up to 750 mg/kg) every 8 hours.

- Patients with $500 \leq ANC < 1000$ at the time of enrollment should receive study drug every 12 hours. Once $ANC \geq 1000$ q8 hour dosing should be instituted.

If patients with GI GVHD cannot tolerate the pills, then MMF should be administered intravenously for the first 3-7 days of therapy and converted to oral MMF as soon as possible after the initial 3-7 days of therapy if oral medications and this limited fluid intake are tolerated.

Duration of Study Therapy

MMF/placebo should be discontinued at Day 56, or when the patient is tapered off steroids, whichever occurs earlier.

GVHD Prophylaxis Medications

Medications such as cyclosporine, tacrolimus, sirolimus (if used as GVHD prophylaxis when acute GVHD developed) should be continued at therapeutic doses adjusted as necessary for

renal, central nervous system (CNS) or other toxicity using conventional management guidelines. The recommended therapeutic trough level of cyclosporine is 200-400 ng/mL measured by whole blood HPLC; institutional levels for other assays. The recommended therapeutic trough level is 5-15 ng/mL for tacrolimus and 3-12 ng/mL for sirolimus.

Topical and Ancillary GVHD Therapies:

Topical therapy for acute GVHD, including skin creams or GI non-absorbable steroids are allowed and should be used according to institutional practices. Use of topical agents for management of acute GVHD will be recorded as a secondary endpoint assessment in this trial.

Ancillary/supportive care measures for acute GVHD such as the use of anti-motility agents for diarrhea, including octreotide, is allowed at the discretion of the treating physician. Use of ursodiol to prevent/ reduce gall bladder sludging, or prevent hepatic transplant complications is also allowed according to institutional guidelines.

2.5. Toxicities and Guidelines for Dose Reduction/Withholding Study Drug

Infection:
Mycophenolate mofetil is potent immunosuppressive agent. Its use has been associated with increased risks of opportunistic infections. In the acute GVHD setting, where corticosteroids and the disease itself further compromise the immune system, particular caution must be paid to the risks of additional infections. See Section 2.9 for supportive care guidelines to minimize infections.

Patients with severe infections may have their study drug held at the attending physician's discretion. Study drug can be reinstituted when the infection episode is controlled and hemodynamic stability restored. Replacement doses must not be given, and administration of the study drug should not be extended. Administration of the study drug will be discontinued permanently if administration is suspended for more than 14 days.

GI toxicity:
Administration of MMF may produce diarrhea, abdominal pain, and vomiting. Gastrointestinal bleeding and bowel perforation have also been described infrequently. If GI toxicity requires medication for control of persistent vomiting or diarrhea (not related to GVHD), a dose reduction to twice a day can be instituted or, if symptoms persist and are severe (Grade 3 or 4), the study drug (MMF/placebo) can be stopped for 48-72 hours. IV MMF can be used in patients experiencing severe GI toxicity to avoid stopping study drug. If GI toxicity does not resolve within 48-72 hours of stopping the study drug, then this toxicity is not likely related to the study medication and the drug should be restarted at the original dose. Administration of the study drug will be discontinued permanently if administration is suspended for more than 14 days. The Protocol Chair or co-Chair should be consulted before discontinuing MMF for GI toxicity.

Myelosuppression:
Use of MMF may be associated with myelosuppression. If the ANC is less than 1000/μL, MMF/placebo dosing should be reduced to every 12 hour dosing. Once ANC ≥ 1000 q8 hour

dosing should be resumed. If the ANC is less than 500/µL, the drug should be discontinued until neutrophil recovery occurs, and restarted at q12 hour dosing. Use of filgrastim or perfilgrastim or sarmograstim or discontinuation of other myelosuppressive agents is allowed. Administration of the study drug will be discontinued permanently if administration is suspended for more than 14 days**.**

Guidelines for Renal Insufficiency:
As free MPA exposure has not been directly correlated with renal dysfunction, patients on renal replacement therapy are excluded from entry on this trial. However, if renal insufficiency (estimated GFR <25) develops or dialysis is needed after study entry, the study drug dose should be reduced from every 8 to every 12 hours.

Hepatic Dysfunction:
No adjustments of MMF/placebo are required for liver dysfunction.

Other Unexpected Toxicities:
Study drug may be held for other CTC v.3 Grade 3-4 toxicities that are considered probably related to MMF/study drug (such as severe apthous ulcers, hypogammaglobulinemia, red cell aplasia) at the discretion of the treating physician. Administration of the study drug will be discontinued permanently if administration is suspended for more than 14 days**.**

2.6. Unblinding

There will be no unblinding or crossover as part of this trial. Unblinding will be allowed only if a critical action is needed, the situation is life-threatening, and the unblinding is deemed to be necessary to the patient's clinical care. Permission for unblinding must be obtained from the medical monitor of the study. Given that there are no data supporting MMF as the preferred second line treatment in patients with inadequate responses to first line treatment, unblinding to allow patients to receive MMF as second line therapy off study will not be allowed.

2.7. GVHD Progression or Non-response

If acute GVHD progresses (new organ involvement or increased organ specific symptoms sufficient to increase the organ stage by one or more) after at least 5 days of study drug administration, or if there is no response (no reduction in any GVHD organ staging) after 14 days of study drug administration, administration of the study drug may be discontinued, and the patient may be treated with alternative secondary GVHD therapy at the discretion of the treating physician.

2.8. Acute GVHD Flare

If acute GVHD flares during taper of prednisone, the dose of steroids may be increased at the discretion of the treating physician as long as this increase is to less than 2.5 mg/kg/day of prednisone (or methylprednisolone equivalent of 2 mg/kg/day), as in this case it will be considered adding a "new agent" and the patient will be scored as a failure.

2.9. Supportive Care Guidelines

In addition to prescribed study drug plus corticosteroids, all patients should receive the following:

- Transfusion support per institutional practice

- Anti-infective prophylaxis against herpes viruses, *Pneumocystis jiroveci,* bacterial and fungal infections should be followed according to standard institutional practices.

- Routine CMV antigenemia/viral load testing by hybrid capture or PCR based methods per institutional guidelines (with preemptive ganciclovir or valganciclovir therapy in patients who develop a positive assay, as per institutional guidelines). CMV testing is recommended weekly through at least Day +100 post transplant.

2.10. GVHD Scoring

As acute and chronic GVHD free survival at Day 56 is the primary endpoint evaluation for the trial, accurate and timely data collection with respect to both acute and chronic GVHD (if present) will be a crucial aspect of this trial.

Weekly acute GVHD organ stage scores, overall clinical grade, biopsy information for GVHD and relevant differential diagnosis will be recorded and reported to the DCC. Organ involvement, biopsy information, staging, differential diagnosis, and GVHD therapy should be documented in the medical record using the BMT CTN GVHD scoring stamp or equivalent (see below).

Symptoms of chronic GVHD, if present, will be reported according to the BMT CTN MOP (Chapter 2) and reported on the GVHD symptom record.

A sample acute GVHD data record suggested for use in this trial is shown below.

Today's BMT CTN 0802 Clinical Acute GVHD Assessment

Today's Date _____   Patient ID/Name _____   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	☐	☐	☐	☐	☐		Current bili: _____	☐	☐	☐	☐	☐	☐	_____

Systemic Agents: ☐ CSA   ☐ Tacrolimus   ☐ Infliximab   ☐ Dacluzimab
☐ Pentostatin   ☐ Sirolimus   ☐ Etanercept   ☐ Open Label MMF
☐ Prednisone   ☐ Methylprednisolone   ☐ Study Drug   ☐ Ontak   ☐ Other _____

Topical Agents: Skin topical steroids ☐ YES   ☐ NO;   Non-absorbed oral steroids (e.g., Budesonide, Entocort) ☐ YES   ☐ NO

Is the patient eating equivalent of one meal/day?   ☐ YES   ☐ NO   Is the patient having formed stools?   ☐ YES   ☐ NO

Does the patient have evidence of chronic GVHD?   ☐ YES   ☐ NO

Current study drug (MMF/Placebo) dose: _____ g ; Frequency: ☐ TID, ☐ BID, or ☐ Other _____ ; Formulation: ☐ PO or ☐ IV

Current steroid dose: Prednisone _____ mg/day or _____ mg/kg/day;   Methylprednisolone _____ mg/day or _____ mg/kg/day

Has the steroid dose been increased to ≥ 2.5mg/kg/day of prednisone (or 2 mg/kg/day methylpred)? ☐ YES   ☐ NO; if yes, date dose increased _____

If yes, reason for dose increase: ☐ flare for GVHD; ☐ Idiopathic Pneumonia Syndrome (IPS); ☐ other (please specify) _____

Code Definitions:

Skin:
0 No rash
1 Maculopapular rash, < 25% of body surface
2 Maculopapular rash, 25-50% of body surface
3 Generalized erythroderma
4 Generalized erythroderma with bullous formation and desquamation

Lower GI (Diarrhea):
0 No diarrhea
1 ≤ 500 mL/day or < 10 mL/kg/day
2 501-1000 mL/day or 10-19.9 mL/kg/day
3 1001-1500 mL/day or 20-30 mL/kg/day
4 > 1500 mL/day or > 30 mL/kg/day
5 Severe abdominal pain with or without ileus, or stool with frank blood or melena

Upper GI:
0 No protracted nausea and vomiting
1 Persistent nausea, vomiting or anorexia

Liver (Bilirubin):
0 < 2.0 mg/dL
1 2.1-3.0 mg/dL
2 3.1-6.0 mg/dL
3 6.1-1.0 mg/dL
4 > 15.0 mg/dL

Signature _____   Date _____   Version 1.0

2.11. Chronic GVHD

Patients developing signs/symptoms of chronic GVHD (cGVHD) will have symptoms recorded on the cGVHD scoring form at the scheduled follow-up visits.

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

*From BMT CTN MOP Chapter 2

2.12. Studies of GVHD Biology

No validated biomarkers exist for acute GVHD. The BMT CTN Biomarkers Committee suggested four recently published biomarkers for validation. Paczesny et al screened plasma with antibody microarrays for 120 proteins in a discovery set of 42 transplant patients that revealed eight potential biomarkers for diagnostic of GVHD.[28] They then measured by ELISA the levels of these biomarkers in samples from 424 transplant patients randomly divided into training (n = 282) and validation (n = 142) sets. Logistic regression analysis of these eight proteins determined a composite biomarker panel of four proteins (interleukin-2-receptor-alpha, tumor-necrosis-factor-receptor-1, interleukin-8, and hepatocyte growth factor) that optimally discriminated patients with and without GVHD. In patients with GVHD, Cox regression analysis revealed that the biomarker panel predicted survival independently of GVHD severity. The authors suggested that the panel of four biomarkers can confirm the diagnosis of GVHD in patients at onset of clinical symptoms of GVHD and provide prognostic information independent of GVHD severity.

If consent for optional future research samples was obtained, plasma will be collected on Day 0 and Day 28 post-treatment and analyzed for the 4-protein biomarker panel. Donor chimerism results recorded at the time nearest to each sample collection will be noted. Remaining plasma sample aliquots will be stored along with an additional Day 56 plasma sample for future biomarker studies. Additionally, whole blood collected from the recipient on Day 0 (representing donor DNA) and buccal swabs for DNA from the recipient will be collected, frozen and stored for future GVHD related studies.

CHAPTER 3

3.   STUDY ENDPOINTS

3.1.   Primary Endpoint

The primary endpoint is the proportion of GVHD-free survival; that is, the percent of patients surviving at Day 56 after enrollment without acute or chronic GVHD and without other systemic agents (or escalation of steroids to $\geq$ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) added for treatment of GVHD.

3.1.1. Staging and Grading of Acute GVHD

In this study we will classify patients by a modified Keystone grading schema.

TABLE 3.1: STAGING

	Stage 0	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
Skin	No rash	Rash < 25% BSA	25-50%	> 50% Generalized erythroderma	Plus bullae and desquamation
Gut	Adult: < 500 ml/day Child: < 10 ml/kg/day	Adult: 500–1000 ml/day Child: 10 -19.9 ml/kg/day	Adult: 1001-1500 ml/day Child: 20 – 30 ml/kg/day	Adult: >1500 ml/day Child: > 30 ml/kg/day	Severe abdominal pain +/- ileus, flank blood or melena
UGI		Severe nausea/vomiting			
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl

3.2.   Secondary Endpoints

Response Definitions:

CR is defined as a CIBMTR score of 0 for the GVHD grading in all evaluable organs. For a response to be scored as CR at Day 56 or later, the participant must still be in CR on that day and have had no intervening additional therapy for an earlier progression, PR or NR.

Partial response (PR) is defined as improvement in one or more organs involved with GVHD symptoms without progression in others. For a response to be scored as PR at Day 28 or later, the participant must still be in PR on that day and have had no intervening additional therapy for an earlier progression, PR or no response (NR).

Mixed response (MR) is defined as improvement in one or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.

Progression is defined as deterioration in at least one organ without any improvement in others.

No response (NR) is defined as absence of any improvement or progression as defined. Patients receiving secondary therapy (including need to re-escalate steroid dose to $\geq$ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) will be classified as non-responders.

3.2.1. Proportion of CR, PR, MR, NR and Progression

Proportion of Complete Response (CR), Partial Response (PR), Mixed Response (MR), No Response (NR) and Progression among surviving patients at Days 14, 28 and 56: Scoring of CR, PR, MR, NR and progression are in comparison to the participant's acute GVHD status (score) on Day 0 of the study.

3.2.2. Proportion of Primary Treatment Failures

Proportion of primary treatment failures among surviving patients at Days 14, 28 and 56: No response, progression, administration of additional systemic therapy for GVHD (or re-escalation of steroid dose to $\geq$ 2.5 mg/kg/day of prednisone (or methylprednisolone equivalent of 2 mg/kg/day), or mortality by Day 14, 28 or 56 post-initiation of treatment will be considered a primary treatment failure.

3.2.3. GVHD Flares Requiring Additional Therapy

Flares are defined as any progression of acute GVHD after an initial response (i.e., earlier CR or PR) that requires re-escalation of steroid dosing, or initiation of additional topical or systemic therapy. While all "flares" will be captured, only flares that require additional systemic therapy (that is additional drugs) or re-escalation of steroids to $\geq$ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] will be counted as failure for the primary endpoint. The rate of all flares before Day 90 will be examined as a secondary endpoint

3.2.4. Immunosuppression Discontinuation

Discontinuation of immunosuppression will be assessed by Day 56, Day 180 and Day 360. The date of discontinuation of corticosteroids will be recorded. In addition, dates for discontinuation of all other systemic immunosuppressive medications (where applicable), including cyclosporine or tacrolimus, sirolimus, etc. for treatment or prevention of acute GVHD will be captured.

3.2.5. Steroid Dose at Days 28 and 56 after Randomization

Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25. Prednisone doses for each patient will be converted to mg/kg. The cumulative prednisone dose for each patient at Day 28 will be calculated by adding the doses (end of each week's dose) for each of the first four weeks of treatment, divided by the

number of days of survival during this interval. The prednisone dose for each patient at Day 28 and Day 56 will be recorded

3.2.6. Incidence of Topical/Non-absorbable Therapy by Day 56

The proportion of patients using either topical skin or topical GI steroids will be calculated.

3.2.7. Chronic GVHD

Chronic GVHD is defined per the BMT CTN Manual of Procedures (MOP) Chapter 2. The incidence of chronic GVHD at 6 and 12 months will be computed for each treatment arm.

3.2.8. Overall and GVHD-free Survival

Overall survival and GVHD-free survival at Days 180 and 360 will be computed for each treatment arm.

3.2.9. Systemic Infections though Day 180

All microbiologically documented infections or significant infections requiring antibiotic/antifungal therapy occurring within six months of initiation of therapy will be reported by site of disease, date of onset, and severity. For definitions see the BMT CTN MOP.

3.2.10. Incidence of EBV

Participating sites are to collect any incidence of EBV-associated lymphoproliferative disorder or EBV reactivation requiring therapy though Day 360.

3.2.11. Disease-free Survival at 6 and 12 Months Post-randomization

Disease-free survival at 6 and 12 months will be computed for each treatment arm. The events for disease-free survival are death and relapse of the underlying malignancy.

3.2.12. Non-relapse Mortality at 6 and 12 Months Post-randomization

Non-relapse mortality at 6 and 12 months will be computed for each treatment arm. The events for non-relapse mortality are death due to any cause other than relapse of the underlying malignancy.

3.2.13. Change in Patient-reported Outcomes from Enrollment to Day 56

Study participants who are able to communicate in English will self-complete the M.D. Anderson Symptom Inventory (MDASI) at enrollment prior to randomization and at Day 56 +/- 7 days. The MDASI is a 19 item instrument that captures 13 symptoms (0="not present" to 10="as bad as you can imagine") and 6 items measuring interference with life from 0 ("did not interfere") to 10 ("interfered completely"). See the MDASI in Appendix E. It provides two

summary scales: symptoms and interference.[29] The MDASI will be scored according to the recommendations of the developers. We estimate it will take 5 minutes to complete the MDASI. Surveys are completed by participants using self-completed instruments as a first choice. If this method of data collection is not possible, then surveys and response options may be read verbatim to participants, either in person or over the phone, to collect data. Although the MDASI has been psychometrically validated in 8 languages, including Spanish, given the exploratory nature of this endpoint we will only administer the MDASI to patients who are able to communicate in English. Surveys may not be completed by surrogates.

NOTE: Long-term follow-up of patients on this study will continue through routine CIBMTR mechanisms.

CHAPTER 4

4.   PATIENT ENROLLMENT AND EVALUATION

4.1.   Enrollment and Randomization

Patients will be registered using the BMT CTN Advantage Electronic Data Capture (EDC). The following procedures shall be followed:

1. An authorized user at the clinical center completes the initial screening by entering patient demographics and Segment A information (inclusion/exclusion criteria) of the Eligibility Form within 72 hours of need of systemic therapy for acute GVHD.

2. If the patient is eligible, a study number and random treatment assignment is generated.

3. A visit schedule based on enrollment date is displayed for printing.

If a connection is interrupted during a randomization session, the process is completely canceled and logged. A backup manual registration and randomization system will also be available to provide for short-term system failure or unavailability.

4.1.1.   Randomization

Patients will be randomized within 72 hours of need of systemic therapy of acute GVHD. Patients will be randomized to MMF versus placebo in a 1:1 ratio. Treatment should be initiated as soon as possible after randomization. A maximum of 48 hours is allowable.

4.2.   Study Monitoring

4.2.1.   Follow-up Schedule

The Follow-up Schedule for scheduled study visits is outlined in Table 4.2.1. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User's Guide.

Follow-up Assessments: The timing of follow-up visits is based on the date of randomization. Following randomization, the Transplant Center can print a Patient Visit Schedule listing target dates for assessments. Weeks 1-8 visits are primarily for acute GVHD scoring. The subsequent visits are for follow-up reports.

Criteria for Forms Submission: Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. Forms that are not received at the DCC within the specified time will be considered delinquent. Transplant Centers can view past due forms via the Web-based data entry system. A missing form will continue to appear until the form is entered into the DCC's master database, or until an exception is granted and

entered into the Missing Form Exception File, as detailed in the Data Management Handbook and User's Guide.

Reporting Patient Deaths: The Recipient Death Information <u>must</u> be entered into the web-based data entry system within 24 hours of knowledge of a patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated.

Center for International Blood and Marrow Transplant Research (CIBMTR) Data Reporting: Centers participating in BMT CTN trials must register pre and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Additionally, CIBMTR pre- and post- transplant Report Forms must also be submitted for all patients enrolled on this trial according to the randomization assigned to the patient at the time of initial registration with the CIBMTR.

Table 4.2.1
FOLLOW-UP SCHEDULE

Assessment Time	Target Day[1] (Days Post-Enrollment)
1 week	7 days
2 weeks	14 days
3 weeks	21 days
4 weeks	28 days
5 weeks	35 days
6 weeks	42 days
7 weeks	49 days
8 weeks	56 days
90 days	90 days
6 months	180 days
12 months	360 days

[1.]Target day range = ±3 days up for Day 7 (subsequent visits through Day 56 must be scheduled weekly).

4.2.2. Assessments

All assessments are considered standard-of-care unless identified below by "*."

Pre-Randomization

1. Recommended biopsy of involved tissue (this is standard of care, not research)

2. History and physical exam including height and weight

3. Pregnancy test (if applicable)

4. Complete acute GVHD staging and grading information including assessments of rash, diarrhea, nausea/vomiting, weight and liver function tests

5. CBC with differential, platelet count

6. Liver function tests (bilirubin, alkaline phosphatase, AST, ALT) plus creatinine

7. Tacrolimus/cyclosporine level (if applicable)

8. M.D. Anderson Symptom Inventory at Day 0 (see Appendix E)

9. (OPTIONAL) Samples for laboratory studies at Day 0 (see Appendix C).* Donor chimerism results to be recorded for the time nearest sample collection.

Post-Randomization

1. Karnofsky or Lansky performance status weekly until Day 56 and at Days 90, 180 and 360

2. Complete acute GVHD staging and grading information including assessments of rash, diarrhea, nausea/vomiting, weight and liver function tests weekly until Day 56, and 3, 6 and 12 months, creatinine weekly until Day 28, and recommended creatinine on Days 35, 42, 49, 56, and 3, 6, and 12 months.

3. Chronic GVHD evaluation (if present) 3, 6 and 12 months

4. CBC with differential, platelet count weekly until Day 56

5. Toxicity evaluation weekly until Day 56

6. Steroid dose weekly until Day 56, and at 3, 6 and 12 months

7. Study drug (MMF/Placebo) dose and formulation weekly until Day 56

8. Topical treatments for GVHD, weekly until Day 56

9. (OPTIONAL) Samples for laboratory studies at Days 28 and 56 (see Appendix C).* Donor chimerism results to be recorded for the time nearest sample collection.

10. Infections requiring therapy up to 6 months after randomization

11. Occurrence of post-transplant lymphoproliferative disorder (PTLD) through Day 360

12. M.D. Anderson Symptom Inventory at Day 56 (see Appendix E)

Table 4.2.2 REQUIRED ASSESSMENTS

	(Day 0)					Days Post Randomization						
	Baseline	7*	14	21	28	35	42	49	56	90**	180***	360***
Suggested biopsy of involved tissue	X											
History and physical exam	X											
Pregnancy test (if applicable)	X											
Karnofsky/Lansky performance status	X	X	X	X	X	X	X	X	X	X	X	X
Acute GVHD evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Chronic GVHD evaluation										X	X	X
CBC with differential, platelet count	X	X	X	X	X	X	X	X	X			
Basic chemistry (creatinine)	X	X	X	X	X	X	X	X-	X	X	X	X
Liver function tests (alkaline phosphatase, bilirubin, AST, ALT)	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity evaluation		X	X	X	X	X	X	X	X			
Steroid dose		X	X	X	X	X	X	X	X	X	X	X
Study drug dose	X	X	X	X	X	X	X	X	X			
Optional blood, and serum for ancillary laboratory studies (see Appendix C)	X				X				X			
Optional buccal Swab (see Appendix C)	X											
M.D. Anderson Symptom Inventory (MDASI)	X								X			
Chimerism (% donor)[1]	X				X				X			

*   +/- 3 days to allow for scheduling flexibility, holidays, etc. Subsequent visits through Day 56 must be scheduled weekly.
**   +/- 14 days to allow for scheduling flexibility
*** +/- 28 days to allow for scheduling flexibility

[1]Donor chimerism results recorded at the time nearest to each sample collection will be noted.

4.2.3. Weekly GVHD Monitoring

GVHD scoring will be performed weekly for 8 weeks from study entry. Days 0, 28 and 56 ($\pm$3 days) scoring must be performed by direct observation at the Transplant Center. Evaluations at other time points may be performed by competent clinicians other than at the Transplant Center but Transplant Center is responsible for collecting all required data.

4.2.4. Serious Adverse Event (SAE) Reporting

Unexpected, grade 3-5 adverse events (AE) will be reported through an expedited AE reporting system via AdvantageEDC. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Unexpected, grade 3-5 AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Expected AEs will be reported using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 at regular intervals as defined on the Form Submission Schedule.

The Data and Safety Monitoring Board will receive summary reports of all Grade 3-5 unexpected adverse experiences on an annual basis.

4.2.5. Study Drug Dose Reduction Monitoring

Because the dosing schedule of MMF in this trial will be more frequent (q8hrs) compared to the previous phase II trial, additional monitoring for potential toxicity will be implemented. Patients who are felt to have potential toxicity related to the study drug (MMF/Placebo) may have their dosing reduced from TID to BID dosing at the discretion of the treating physician as outlined in Section 2.5. The dose and schedule of MMF/placebo will be recorded weekly. After 20 and 40 patients have been enrolled, interim analyses will be performed to assess the incidence of sustained dose reduction from TID for reasons of toxicity in the MMF and placebo arms by Day 28. Sustained dose reduction will be defined as reduction from TID dosing for reasons of toxicity for the duration of at least 1 week without re-escalation of dose. If the incidence of sustained dose reduction in the MMF arm is >30% higher than that observed in the placebo arm, the protocol team will consult with the Data and Safety Monitoring Board and consider amending the starting MMF/placebo dose to BID dosing for the entire study.

4.3. Discontinuation Criteria

Study drug therapy (MMF or placebo) shall be discontinued and not re-instituted if any one of the following criteria is met. The patient will be taken off study drug therapy at that point, but still followed for primary and secondary study endpoints. A response assessment will be made at the time of therapy discontinuation and at subsequent defined study endpoints. The patient will not be replaced on study. Note: though the study drug will be discontinued in the following circumstances, corticosteroid dosing will be managed as clinically indicated by the treating physician. Follow-up data will be required unless consent for data collection is withdrawn:

- Additional systemic GVHD therapy is added for disease progression or non-response

- Steroid dose is escalated to ≥ 2.5 mg/kg/day of prednisone (or methylprednisolone equivalent of 2 mg/kg/day) for disease progression or non-response

- Development of toxicity that requires withholding of study medication for more then 14 days (see Section 2.5 for details of dose modifications for toxicity)

CHAPTER 5

5.   STATISTICAL CONSIDERATIONS

5.1.   Study Design

The study is designed as a Phase III, randomized, double-blind, multicenter, prospective comparative study of steroids + MMF vs. steroids + placebo for treatment of acute GVHD. The target enrollment is 372 patients.

5.1.1.   Accrual

It is estimated that three years of accrual will be necessary to enroll the targeted sample size. Both Core and non-Core Centers will enroll patients on this study. Accrual will be reported by race, ethnicity, gender, and age (pediatric patients will be defined as < 18 years).

5.1.2.   Randomization

Randomization will be performed in a 1:1 ratio using random block sizes for the two arms. Randomization will be stratified by transplant center and grade of GVHD (I-II vs. III-IV) at study entry.

5.1.3.   Primary Endpoint

The primary endpoint is the GVHD-free survival proportion at Day 56 post randomization. The primary analysis will be performed using the intent-to-treat principle so that all randomized patients will be included in the analysis. Death, lack of CR at Day 56, initiation of additional therapy, or development of chronic GVHD will be considered failures for this endpoint. Flares of acute GVHD after achieving CR will not result in a failure for the primary endpoint as long as the patient still achieves CR at Day 56 and does not need additional therapy.

5.1.4.   Primary Hypothesis

The primary null hypothesis of the study is that there is no difference between the GVHD-free survival proportions for MMF compared to the placebo arm.

$$H_o: \quad p_{MMF} = p_{PL}$$
$$H_a: \quad p_{MMF} \neq p_{PL}$$

5.2.   Sample Size and Power Considerations

GVHD-free survival at Day 56 post-randomization will be compared between the MMF and placebo using the Z test for comparing two binomial proportions. The final analysis will be performed after all patients have been followed for a minimum of 56 days post-randomization.

Sample size and power considerations are based on estimates from BMT CTN Protocol 0302, the randomized Phase II study on which this Phase III study is based. In BMT CTN 0302, the estimated Day 56 GVHD-free survival was 71% for the MMF arm (n=44) and 47% for the three combined non-MMF arms (n=134). Although the observed difference in GVHD-free survival proportions was 24%, this was based on a small sample size for the MMF arm. In this study, we target a more modest difference of 15%, which would still be considered clinically relevant. The sample size of 186 patients per group, or 372 total, is sufficient to maintain type I error of 5% across all planned interim analyses (see below) while providing 80% statistical power for a two-sided test to detect an increase in the GVHD-free survival proportion at Day 56 from 0.47 in the placebo arm to 0.62 in the MMF arm.

5.3. Interim Analysis and Stopping Guidelines

Interim analyses for efficacy and futility will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed Data and Safety Monitoring Board (DSMB) at approximately six month intervals. Monitoring of key safety endpoints will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures.

5.3.1. Interim Analysis for Efficacy and Futility

Analyses will be performed as described below for the primary endpoint. Toxicity, adverse events, and other safety endpoints will be monitored regularly and reported to the DSMB at each interim analysis.

At each interim analysis time point, a two-sided test to detect either an increase or decrease in the GVHD-free survival proportion at Day 56 will be performed. The test statistic based on the Z test comparing binomial proportions will be compared to the critical values shown below. All patients with at least 56 days of follow-up prior to the time of the interim analyses will be used to compute this statistic. If the test statistic is outside the continuation range, the DSMB will discuss the continuation of the trial.

In order to preserve the over-all type I error rate at 5%, efficacy and futility stopping rules will be constructed using error spending functions for both the type I error rate alpha and the type II error rate beta. The error spending function defined by $f(t)=\min(\alpha t^3,\alpha)$, which approximates the O'Brien-Fleming efficacy boundary, will be used for both error rates, except that stopping for futility will not be allowed until half of the patients are evaluable. This error spending function approach permits necessary flexibility in the scheduling of interim analyses based on the rate of accrual and the timing of DSMB meetings.

As an example, Table 5.3a shows the critical values and cumulative error rates for tests conducted every six months starting with the 8th month after the study opens to enrollment. The column labeled "followed to 56 days" shows the expected number of individuals who have reached the 56-day post-randomization follow-up time point, assuming uniform accrual over a three-year period. The fraction of patients followed to 56 days, as compared to a denominator

comprised of the total sample of 372, quantifies the "statistical information" from which the critical values are computed.

TABLE 5.3a – CRITICAL VALUES

Calendar Time (Months)	# of Patients Followed to 56 Days	Stop for Futility if |Z|<	Stop for Efficacy if |Z|>	Cumulative Type I Error	Cumulative Type II Error
8	62	-	4.30	.0002	-
14	124	-	3.22	.0018	-
20	186	0.28	2.86	.0062	0.0250
26	248	0.74	2.58	.0148	0.0593
32	310	1.38	2.30	.0289	0.1157
38 (Final)	372	2.05	2.05	.0500	0.2000

5.3.2. Operating Characteristics of the Design

The statistical power to reject the null hypothesis of equal Day 56 GVHD-free survival is shown in Table 5.3b under a variety of scenarios, using the Z test comparing the Binomial proportions. These simulation results assume that the interim analyses are conducted at equally spaced information times. Also shown are the stopping probabilities for efficacy or futility at each of the planned interim analyses. This table shows that the target sample size of 372 patients has >80% power to detect a 15% improvement in GVHD-free survival.

TABLE 5.3b – POWER TO REJECT THE NULL HYPOTHESIS UNDER VARIOUS SCENARIOS

Proportion Alive and GVHD-Free at Day 56		Reason for stopping	Probability of Stopping at Interim and Final Analyses By number of patients evaluable at time of Scheduled Analysis						Overall (Cumulative) Power
Placebo	MMF		62	124	186	248	310	372	
0.47	0.47	Efficacy	0	0.002	0.004	0.008	0.014	0.021	0.049
		Futility	0	0	0.175	0.372	0.304	0.1	
0.47	0.52	Efficacy	0	0.005	0.013	0.025	0.043	0.065	0.151
		Futility	0	0	0.14	0.284	0.28	0.145	
0.47	0.57	Efficacy	0.001	0.02	0.054	0.098	0.138	0.153	0.464
		Futility	0	0	0.068	0.13	0.18	0.157	
0.47	0.62	Efficacy	0.005	0.07	0.161	0.216	0.213	0.145	0.809
		Futility	0	0	0.021	0.033	0.058	0.078	
0.47	0.67	Efficacy	0.014	0.18	0.306	0.263	0.151	0.056	0.969
		Futility	0	0	0.004	0.004	0.008	0.015	

* from simulation with 100,000 replications

5.3.3. Guidelines for Safety Monitoring

Monitoring of a key safety endpoint will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guideline serves as trigger for consultation with the DSMB for additional review.

The key safety endpoint for this study is mortality. The rate of mortality will be monitored up to 28 days post-randomization. Monitoring will be performed monthly beginning after the third month of enrollment until enrollment is closed. At least three events must be observed in order to trigger review. Each month, the null hypothesis that the 28-day mortality rate is less than or equal to 7.5% is tested. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be used for monitoring, as described in greater detail below and in Appendix D.

This sequential testing procedure conserves type I error at 5% across all of the monthly examinations. The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of endpoints (e.g., patients experiencing death). The continuation region of the SPRT is defined by two parallel lines. Only the lower boundary will be used for monitoring to protect against excessive 28-day mortality. If the graph falls below the lower boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment reaches the maximum of 186 patients.

This procedure assumes a censored exponential distribution for the time until death during the first 28 days, and censors follow-up time after 28 days. Only deaths that occur on or before the patient has been followed for 28 days are counted. Total time on study is computed as time from registration to death, or to 28 days, whichever comes first, summed for all patients on study.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRTs:

- A SPRT contrasting 7.5% versus 22.5% 28-day rate of mortality results in decision boundaries with a common slope of 6.695 and a lower intercept of –12.691, with nominal type I and II errors of 9% and 15%, respectively.

The actual operating characteristics of the truncated test, shown in Table 5.3c, were determined in a simulation study that assumed uniform accrual of 186 individuals over a three-year time period, and exponential time to failure after randomization.

TABLE 5.3c: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

Day 28 MORTALITY

True 28-Day Rate	7.5%	12.5%	17.5%
Probability Reject Null	0.052	0.449	0.929
Mean Month Stopped	35.4	25.5	11.9
Mean # Endpoints in 100 Days	13.3	16.0	10.3
Mean # Patients Enrolled	178.0	129.0	61.2

For example, the testing procedure rejects the null hypothesis in favor of the alternative 5% of the time when the true 28-day mortality rate is 7.5%, and 93% of the time when the rate is 17.5%. This corresponds to a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.07$. When the true 28-day mortality rate is 17.5%, on average, the DSMB will be consulted 12 months after opening, when 10 events have been observed in 61 patients.

5.3.4.   Safety Analysis

The reporting of serious adverse events will be consistent with standard BMT CTN procedures. All reported serious adverse events potentially associated with study drug will be carefully examined with respect to the severity and relationship to study drug. The type and severity of adverse events will be described.

5.3.5.   Monitoring Guidelines for Dose Reduction

Rates of dose reduction will be compared between the blinded study arms early in accrual to determine whether there is evidence of a differential rate. Such a difference would indicate that the starting dose should be decreased from 3 times daily to 2 times daily. Dose reduction is defined as one week of sustained dose reduction from TID dosing through Day 28. It is anticipated that rates of dose reduction will be low in the placebo arm, approximately 10-20%, and the monitoring rule is designed to identify a 30% absolute difference in dose reduction rates between the two study arms with 80% power. If the monitoring rule is triggered, the DSMB will be notified and asked to review unblinded toxicity data in the two arms to assess whether the starting dose of MMF should be decreased.

The dose reduction stopping rule is based on an O'Brien-Fleming boundary for the Z statistic comparing the probabilities of dose reduction by Day 28 between the two groups, with two looks at the data. Death without dose reduction will be treated as the competing risk, and the cumulative incidence estimator will be applied to all randomized patients to estimate the probability of dose reduction in each group. Dose reduction rates will be compared after 20 and 40 patients are randomized and followed for 28 days in each arm. Such early assessment will allow for at least 75% of the patients to be treated in the same way and with the same starting dose. Enrollment will not be put on hold after the 20th and 40th patients are enrolled unless the

test statistic is close enough to the boundary that the additional follow up could potentially trigger the stopping rule.

Details of the stopping rule are given in Table 5.3d. Also contained in the table are the cumulative probabilities of triggering DSMB review as a function of the increase in dose reduction rates, assuming a 20% baseline dose reduction rate in the placebo arm. These stopping probabilities are computed by simulating simple binomial proportions for the dose reduction rate in each group; in practice, the stopping rule would be based on the cumulative incidence estimator using all patients, including those with less than 28 days of follow-up. The binomial calculation provides a conservative estimate of the power for this stopping rule. The stopping rule controls the type I error rate at 5% if there is no increase in the dose reduction rates, and has more than 80% power to identify a 30% increase in the dose reduction rates within 40 patients. The type I error rate is still controlled and the power is higher if the baseline dose reduction rate is 10% (results not shown).

TABLE 5.3d: MONITORING RULE AND OPERATING CHARACTERISTICS FOR DOSE REDUCTION RATES IN THE FIRST 40 PATIENTS PER ARM

# of patients per arm	Stop if	Cumulative stopping probability for absolute difference in dose reduction rates of			
		0%	20%	25%	30%
20	$|Z|>2.80$	0.006	0.114	0.200	0.298
40	$|Z|>2.05$	0.050	0.512	0.677	0.822

5.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, risk status, acute GVHD grade at enrollment, donor age, donor gender, and donor ethnicity. Between group comparisons will be performed for continuous variables via a t-test and for categorical variables, via the chi-square test.

5.5. Analysis of Secondary Endpoints

5.5.1. Proportion of CR, PR, MR, NR and Progression

Proportions of Complete Response (CR), Partial Response (PR), Mixed Response (MR), No Response (NR) and Progression at Days 14, 28 and 56 will be compared between the treatment groups using the chi-square test.

5.5.2. Proportion of Primary Treatment Failures among Surviving Patients

Proportion of primary treatment failures among surviving patients at Days 14, 28 and 56 will be compared using the Z test for comparing binomial proportions.

5.5.3. GVHD Flares Requiring Additional Therapy

The proportion of patients experiencing a flare after an initial response will be evaluated at Day 90 and compared between treatment groups using the Z test for comparing binomial proportions. This will be done both for all flares as well as flares that require additional systemic therapy.

5.5.4. Immunosuppression Discontinuation

The incidence of discontinuation of immunosuppression will be computed separately in each treatment group using the cumulative incidence curve, with death prior to discontinuation as the competing risk. Pointwise 95% confidence intervals will be provided at Day 56, Day 180, and Day 360. Comparison of the cumulative incidence curves between treatment will be done using Gray's test.

5.5.5. Steroid Dose at Days 28 and 56 after Randomization

The median and range of steroid doses at each time point will be provided separately for each treatment group. The median steroid dose will be compared between treatment groups using the Wilcoxon rank sum test.

5.5.6. Incidence of Topical/Non-absorbable Therapy by Day 56

The proportion of patients using topical/non-absorbable therapy by Day 56 will be compared between the treatment groups using the Z test for binomial proportions.

5.5.7. Chronic GVHD

The incidence of chronic GVHD will be computed using the cumulative incidence estimator, treating death prior to chronic GVHD as a competing risk. Pointwise confidence intervals will be provided at 6 and 12 months, and the cumulative incidence curves will be compared using Gray's test.

5.5.8. Overall and GVHD-free Survival

Overall survival will be computed using the Kaplan-Meier estimator. Pointwise confidence intervals will be provided at Days 180 and 360. Survival curves will be compared between treatment groups using the log-rank test. GVHD-free survival will be estimated using simple proportions of patients alive and without GVHD if there is no censoring prior to 180 or 360 days. If there is censoring, the proportion of patients alive and without GVHD will be estimated in each treatment using multi-state model techniques.[30]

5.5.9. Systemic Infections though Day 180

Frequencies of infections will be tabulated by site of disease, date of onset, and severity. The time to first serious infection will be described using the cumulative incidence function with death as the competing risk, and compared between treatments using Gray's test.

5.5.10. Incidence of EBV

The incidence of EBV-associated lymphoproliferative disorder or EBV reactivation therapy through Day 360 will be described using the cumulative incidence function, treating death as the competing risk. Cumulative incidence curves will be compared between treatments using Gray's test.

5.5.11. Disease-free Survival at 6 and 12 Months Post-randomization

Disease-free survival will be estimated using the Kaplan-Meier method, treating death or relapse of malignancy as events in patients with malignancies. This outcome will be compared between the two treatment groups using the log-rank test.

5.5.12. Non-relapse Mortality at 6 and 12 Months Post-randomization

Non-relapse mortality will be estimated using the cumulative incidence method, treating relapse as the competing risk. The cumulative incidence curves for non-relapse mortality will be compared between the treatments using Gray's test.

5.5.13. Change in Patient-Reported Outcomes from Enrollment to Day 56

Participant self-reported measures will be assessed at two time points using the MDASI at enrollment and at Day 56. The MDASI will be scored according to the recommendations of the developers. We will explore the range of scores to assess the medians, means and standard deviations observed. Using repeated measures longitudinal models, we will use PROC MIXED to explore changes over time and major domains that differ between patients on the two trial arms. In exploratory analyses, we will also investigate the clinical relevance of particular items in the MDASI, including the items which correlate with different organ manifestations of acute GVHD and the items most sensitive to change when acute GVHD improves objectively.

APPENDIX A

HUMAN SUBJECTS

APPENDIX A

HUMAN SUBJECTS

Subject consent: Candidates for the study will be identified as described in Chapter 4 of the protocol. The Principal Investigator or his/her designee at each transplant center will contact the candidates and enroll them onto the study. The study coordinator at each center will provide the patient with information about the purpose of the study and obtain consent. The Network will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Internal Review Board (IRB). The DCC will verify the adequacy of the consent forms. Each center must provide evidence of IRB approval.

Confidentiality: Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

Participation of women, children, minorities and other populations: Women, children and ethnic minorities will be included in this study.

Accrual will be monitored within each center with the expectation that the enrolled patient population is representative of the transplanted patient population at each center. Representation will be examined by comparing gender, race, ethnicity and age distributions. Accrual of minority patients will be expected to be in proportion to the number of minority patients transplanted at each center. The DCC and NHLBI will discuss enrollment anomalies with the centers.

APPENDIX B

INFORMED CONSENTS
AND
EDUCATIONAL MATERIAL

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

ASSENT TO PARTICIPATE IN RESEARCH

Informed Consent to Participate in Research

Your Name: _____

Study Title: A Multi-Center, Randomized, Double Blind, Phase III Trial Evaluating Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as Initial Systemic Treatment of Acute GVHD.

Protocol: 0802

Investigator: Javier Bolaños Meade, M.D.
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
1650 Orleans Street
Baltimore MD 21231
Phone: 410-614-6398.

Co-Investigator: Vincent T. Ho, M.D.
Dana Farber Cancer Institute
44 Binney Street
Boston MA 02115
Phone: 617-632-5938

**Transplant Center
Investigator**: _____

Sponsor: The National Institutes of Health (NIH) gave financial support for this research study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Introduction

You are invited to join a research study. This study will evaluate a GVHD treatment that includes the use of prednisone (a corticosteroid) and either: a placebo (sugar pill) or the study drug, mycophenolate mofetil (MMF). The placebo is not a treatment and will have no effect on your condition. The placebo or MMF will be randomly assigned to you.

If you decide to join the study, you will receive either steroids and MMF, or steroids and a placebo. If you choose not to join the study, you will receive standard treatment.

This Consent Form will tell you about the purpose of the research, its possible risks and benefits, other options available to you, and your rights as a participant in the study. Please take your time to make your decision.

Everyone who takes part in research at [insert facility name] should know that:

- Being in any research study is voluntary.

- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.

- If you join the study, you can quit the study at any time.

- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].

- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.

- You can ask questions now or any time during the study.

- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

1. Background

This research study is sponsored by The National Institutes of Health (NIH) through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The goal of this study is to find a better treatment for acute GVHD in people who have had an allogeneic blood stem cell transplant.

Acute GVHD is a medical condition that can become very serious. Acute GVHD is a common development after allogeneic stem cell transplant. It happens when the donor cells attack and damage your tissues after transplant. Acute GVHD often causes:

- Skin rashes

- Nausea (feeling sick to your stomach)

- Vomiting (throwing up)

- Abdominal pain

- Diarrhea

- Liver damage that can cause inflammation in the liver or jaundice (yellowing of the skin or eyes)

Patients with acute GVHD are at risk to develop chronic GVHD. Chronic GVHD may also cause damage to other organs. Acute and chronic GVHD may be bad enough to cause death.

Corticosteroid (or steroid) medications, such as prednisone, are the standard of care for early treatment of GVHD. However, less than half of patients will become free of acute GVHD when steroid treatment is used alone. Information from a BMT CTN study suggests that Mycophenolate mofetil or "MMF" in combination with standard steroid therapy may lower the risk of developing GVHD.

MMF is a drug that blocks the growth of the immune cells (T lymphocytes), which are believed to cause GVHD. MMF is approved by the U.S. Food and Drug Administration (FDA) to prevent rejection after organ transplant. MMF has been used for years as a treatment for GVHD that does not respond to standard corticosteroid therapy, or to prevent GVHD after allogeneic stem cell transplant.

2.   Purpose

You are invited to join this research study because you have developed acute graft-versus-host disease (GVHD) and your doctor feels that treatment for the GVHD is necessary.

We will measure how the addition of MMF compares long-term to the standard treatment of steroids for acute GVHD. Specifically, we also want to know if MMF will:

- Reduce the symptoms and signs of acute GVHD, or

- Eliminate acute GVHD completely.

MMF will be compared to a placebo (sugar pill) to learn if it will reduce or eliminate your acute GVHD when added to the standard treatment of steroids.

We also want to collect extra blood samples and mouth swabs for future research on GVHD. You may take part in this additional study if you want to. You can still be part of the main study even if you do not want to donate extra blood samples.

3.   Right to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:
[insert contact info]

Being in this study is voluntary. You can choose to not be in this study, or leave this study at any time. If you choose to not take part or to leave this study, your regular medical care will not be affected in any way. This includes standard care for your acute GVHD.

If you decide to leave this study after taking the study treatment, or are asked to leave by your doctor for medical reasons, you will need to come back to the doctor's office for tests for your safety. Even if you withdraw from the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

Your study doctor and study staff will be available to answer any questions that you may have about your participation in, or your withdrawal from this study.

4.   Procedures

Before you join the study, we will ask you about your medical history, and any medications you may be taking. It is important that you do not participate in the study if you suffer from an allergy to mycophenolate mofetil (MMF); or if you are pregnant, breastfeeding or are likely to become pregnant during the study.

Your doctor will do a number of tests to determine if you are able to join this study. These tests include:

- A physical exam that also measures the stage of your GVHD.

- Your ability to do regular daily activities (performance status).

- Routine blood tests to check your blood counts, how well your liver and kidneys work, and levels of GVHD prevention medications in your blood (if it applies to you).

- Pregnancy test (if it applies to you).

If you decide to join, we will ask you to sign this Consent Form, and you will get a copy of the signed form to keep.

There will be two study groups. One group will receive MMF and the other group will receive the placebo. Both groups will receive the standard treatment of steroids. About 372 patients will participate at several centers around the country. Your study participation will last about 12 months and you will be required to attend the clinic at least 8 times during the first 8 weeks of the study.

You may take the assigned placebo or MMF for up to 8 weeks. Once you stop taking the placebo or MMF, the study team will follow your health for up to 12 months after you first join the study.

Another part of the study will ask questions about your symptoms. This information will be collected at two times: enrollment on the study and approximately 56 days later. The survey has 19 questions and should take less than 5 minutes to complete. You may skip any questions you wish.

Randomization

We will randomly assign you to one of two study groups using a computer. This means that you will be put into a group by chance. It is like the flip of a coin or drawing names out of a hat. You will have an equal chance of being placed in either group.

You will not be told to which group you are assigned. Study staff at your visits will not know your group assignment either. We can find out which group you are assigned to if we ever need to know to protect your safety.

Additional Study Visits and Procedures

We will give you a placebo or MMF along with prednisone or methylprednisolone (steroids), which are standard treatment for acute GVHD. The placebo and MMF come in the form of pills. If you cannot take pills, the placebo or MMF can be given to you through your vein (IV infusion).

You will take your assigned drug three times each day for up to 8 weeks. We will watch you closely for:

- Signs of GVHD

- Changes in your blood counts, liver and kidney function

- Any side effects

- Signs of infection

Weekly Health Evaluations

We will evaluate your health every week for 8 weeks once you start taking your study drug. At your week 4 evaluation we will collect extra blood samples if you agreed to participate in the optional research sample portion of this study. Each health evaluation will include tests to evaluate your:

- GVHD stage

- Ability to do daily activities (performance status)

- Blood counts, liver and kidney function, and levels of GVHD prevention medications in your blood (if it applies to you)

- Development of any side effects or signs of infection

These tests and how often they are scheduled are standard care for patients with acute GVHD and would be done even if you were not part of this study.

Monthly Health Evaluations

Once you finish the 8 weeks of study treatment, we will evaluate you at approximately 3, 6 and 12 months after you first joined the study. During these visits, we will evaluate your:

- GVHD stage

- Ability to do daily activities (performance status)

- ▪ Routine blood tests including your blood counts, how well your liver and kidneys work, and levels of GVHD prevention medications in your blood (if it applies to you)

The evaluations at week 4 and week 8 must be done at the transplant center. Other exams and tests may be done at the transplant center or at a local doctor's office if your condition improves and it is closer to where you live, at the discretion of your transplant doctor.

These tests and how often they are scheduled are standard care for patients with acute GVHD and would be done even if you were not part of this study.

5.   Alternative Treatments

Current available treatments which may be used to treat acute GVHD include:
- ▪ Corticosteroids without the study drug (standard treatment for GVHD)
- ▪ Participation in another clinical trial (if available, check with your doctor)

Every treatment option has benefits and risks. Your study doctor will discuss these options with you. If you decide not to participate in this research study, your medical care will not be affected in any way.

6.   Risks and Discomforts

a.) <u>Side Effects of Study Drugs</u>
All drugs can have side effects, including the standard therapy for GVHD (steroids) and MMF being tested in this study. Your doctor will watch you carefully and will change your treatment if side effects develop. MMF used in addition to steroids for GVHD is an experimental treatment, but information has already been collected on its effects in people. We have a limited amount of information about children (pediatric patients) treated with MMF for GVHD.

Placebo:
The placebo will look and taste like MMF (mycophenolate mofetil) but it is not a drug. The placebo is not expected to have any side effects and it will have no effect on your condition.

Mycophenolate Mofetil (MMF):
MMF is a potent immunosuppressive drug that blocks the growth of the immune cells that can cause GVHD.

Risks and side effects related to MMF include those that are:

<u>Common</u> (more than 20% of patients)
- ▪ Infection
- ▪ Upset stomach, including nausea

<u>Less common</u> (less than 20% of patients)
- Low blood counts
- Vomiting
- Diarrhea

<u>Rare but serious </u>(less than 2-3% of patients)
- Serious injury to your gut (digestive tract), including bloody stools and vomit
- Secondary cancers, such as lymphoproliferative disease or lymphoma
- Serious infections of the brain
- Risk to a baby in pregnancy
- Progressive Multifocal Leukoencephalopathy (PML)

b.) <u>Infections</u>

Because GVHD is caused by an immune attack on your tissues from the transplanted donor cells, all treatments for GVHD include drugs to control (suppress) that immune attack. There is a higher risk of infection in patients with GVHD and any treatment for GVHD may also increase your risk of infection. Infections may be bad enough to cause death.

You will need to take several antibiotics to prevent infection. You will also be watched carefully for any infections while you are being treated for GVHD. Tell your doctors promptly if you get a fever, chills, cough or any other symptoms that might be a sign of an infection.

c.) <u>Risks of Other Procedures Including Blood Draws</u>

There are no major risks associated with drawing blood. Having your blood drawn can be uncomfortable and can sometimes cause a bruise. In rare cases, a blood draw can cause fainting. Only trained people will draw your blood.

d.) <u>Reproductive Risks</u>

MMF may cause injury or birth defects if it is taken during pregnancy. Because of this, it is important that you are not pregnant or breast-feeding and do not become pregnant during the course of the study.

If you are a woman and pregnancy is a possibility, you will need to take a pregnancy test before you start the study. You should discuss ways to not become pregnant while you are participating on the study. Unless you have been in menopause for at least 12 months in a row, pregnancy is a possibility.

MMF can make birth control pills less effective. You must either use abstinence or two non-hormone forms of birth control (such as a condom, diaphragm, or spermicide). You must continue to prevent pregnancy before and during your treatment with MMF, and for at least 6 weeks after your treatment ends.

Ask your doctor about abstinence or the most effective non-hormonal forms of birth control and which options are best for you. If you do become pregnant while you are in the study, you should tell your doctor right away. You will be removed from the study

drug and you will receive information on medical care, if you need it. You must not continue to take the study drug if you are pregnant.

e.) <u>Unforeseen Risks</u>
New risks might appear at any time during the study that are different from the risks listed in this Consent Form. We will promptly tell you of any new information that may affect your decision to participate.

f.) <u>Other Treatments or Medications</u>
Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking.

This includes non-prescription medications, vitamins and herbal treatments. It is also important that you tell the study staff about any changes to these medications during your participation in the study.

g.) <u>Risks of completing the survey</u>
Completion of the survey about your symptoms will not cause you any physical discomfort, although it is possible that you will find some of the questions or topics upsetting. If you do, there will be someone available to speak with you. They will be able to refer you to appropriate counselors or other support people.

7.   Possible Benefits

Taking part in this study may or may not make your health better. While doctors hope that MMF in combination with steroids will be more useful against acute GVHD compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about MMF in the treatment of acute GVHD. This information could help future allogeneic transplant patients

8.   New Information Available During the Study

During this research study, new information about the study drug or the risks and benefits of the study may become known to the study doctors. If this happens, they will tell you about the new information.

The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study. If this happens, the study doctor will stop your participation in the study and you will be offered all available care to suit your needs and medical conditions.

9.   Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy.

Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Your study number is not related to your name, social security number or medical record number at [insert facility name].

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- The Center for International Blood and Marrow Transplant Research (CIBMTR)

- The National Marrow Donor Program (NMDP)

- The Food and Drug Administration (FDA)

- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)

- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), and

- Other authorized study organizations.

We will not identify you by name in any publications or reports coming from these organizations or groups.

10.   Ending Your Participation

The study doctor or the study sponsor may stop the study at any time. We may ask you to leave the study if you do not follow directions or if you suffer from side-effects of the treatment. If you are asked to leave the study, the reasons will be discussed with you.

Possible reasons to end your participation in this study include:

- You do not meet the study requirements.

- You need a medical treatment not allowed in this study.

- The study doctor decides that it would be harmful to you to stay in the study.

- You are having serious side effects.

- You become pregnant.

- You cannot keep appointments or take study drugs as directed.

- The company making the study drug/placebo is no longer able to supply it.

- The study is stopped for any reason.

11.   Physical Injury as a Result of Participation

It is important that you tell your study doctor or study staff if you feel that you have been hurt or injured because of taking part in this study. You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. This study will not pay for medical treatment. In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

12.   Compensation or Payment

You will not be paid for your participation in the research study. You will not get compensation or reimbursement for any extra expenses (travel, meals, etc.) you may have through your participation on this trial.

13.   Costs & Reimbursements

Most of the visits for this research study are standard medical care for patients with GVHD and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study.

You or your insurance will not be charged for the study medication (MMF or placebo) or for the optional blood and DNA samples for research on this study. The study drug will be provided free of charge while you are participating in the study.

14.   Ethical Review

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

15.   Further Information

If you need any information about this study, or if you have any problems while you are participating in this study you can contact the study doctor or his/her staff. They may be contacted at the telephone numbers listed here:

[Insert name and contact details].

16.   Independent Contact

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[Insert appropriate contact details]

Please note: This section of the informed Consent Form is about an additional research study that will be done with people who are taking part in the main study. You may take part in this additional study if you want to. You can still be a part of the main study even if you say 'no' to take part in this additional study.

Blood and DNA Samples for Research
We are asking your permission to collect and store extra blood and a DNA sample. These samples will be used for future research on GVHD tests and treatment. DNA is a molecule that contains a person's genetic information. We would collect a sample of your DNA by using a mouth swab.

DNA from your stored blood and DNA samples and your health information might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small genetic changes that are more common in people with a particular disease than in people without the disease. Each study can look at hundreds of thousands of genetic changes at the same time. Researchers use data from this type of study to find genes that may add to a person's risk of developing a certain disease. If your coded genetic and clinical information is used in such a study, the researcher is required to add the DNA test results and non-identifying information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Procedures

- We will collect a sample of your DNA by using 4 mouth swabs on Day 0.

- We will collect blood samples at three different dates in the study: Pre-treatment baseline at Day 0, and then on Day 28 and Day 56 after treatment begins.

- The amount of blood collected from you is small – about 2 teaspoons (10-12mL) each time.

- These samples will be used for protocol-defined studies and may also be stored indefinitely for future research.

Withdrawal

If you agree to allow your blood and DNA samples to be used for research, you can change your mind at any time. If you change your mind, please contact [the Principal Investigator at your transplant center] in writing to state that you are withdrawing permission for your blood to be used for research. His/her mailing address is on the first page of this Consent Form. Any unused tissue will be destroyed if you withdraw your permission. **If you choose not to participate in this additional research there will be no change in your care**.

Benefits

You will not benefit directly from providing blood and DNA samples for this study.

Risks

There are no major risks associated with drawing blood. Having your blood drawn can be uncomfortable and can sometimes cause a bruise. In rare cases, it can cause fainting. Only trained people will draw your blood.

Confidentiality and Your Medical Information

The results of GVHD research done with your blood and DNA will not be part of your medical record and will not be shared with you.

If you agree to allow your blood and DNA samples to be used for research, they will be collected confidentially and your name will not be on the tubes. Only the study doctors or staff working with them will study the results from your blood and DNA samples.

Information gained from research on your blood and DNA may be used to develop of diagnostic procedures or new treatments for GVHD in the future. Your blood will not be sold to any person, institution, or company for financial gain or profit.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, make your selection by checking one of the boxes. If you have any questions, please talk to your doctor or nurse, or call our research review board at [IRB's phone number].

No matter what you decide to do, it will not affect your care.

❑   I agree to allow my blood and DNA to be used for future research.

❑   I do not agree to allow my blood and DNA to be used for future research.

_____   _____
Signature   *Date*

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purposes

A. Purpose:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center, Randomized, Double Blind, Phase III Trial Evaluating Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as Initial Systemic Treatment of Acute GVHD.

B. Individual Health Information to be Used or Disclosed

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after treatment (for example: blood tests, biopsy results)

C. Parties Who May Disclose My Individual Health Information

The researcher and the researcher's staff may collect my individual health information from: (List hospitals, clinics or providers from which health care information can be requested).

D. Parties Who May Receive or Use My Individual Health Information

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
  Dr. Javier Bolaños Meade, Principal Investigator

  Dr. Vincent T. Ho, Co-Principal Investigator

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH)

- Study sponsors
  Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data and coordinating center

- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)

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[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

- ▪ <u>U.S. government agencies that are responsible for overseeing public health concerns</u> such as the Centers for Disease Control (CDC) and federal, state and local health departments.

E. Right to Refuse to Sign this Authorization

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study. My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. Right to Revoke

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. Potential for Re-disclosure

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. This authorization does not have an expiration date.

TITLE: A Multi-Center, Randomized, Double Blind, Phase III Trial Evaluating
Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as
Initial Systemic Treatment of Acute GVHD

I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me. I understand that I will be given a copy of this signed Consent Form

_____   _____

Participant Name   *Date*

_____   _____

Participant Signature   *Date*

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____   _____

Counseling Physician   *Date*

_____   _____

Signature of Counseling Physician   *Date*

Assent to Participate in Research

Study Title: A Multi-Center, Randomized, Double Blind, Phase III Trial Evaluating
              Corticosteroids with Mycophenolate Mofetil vs. Corticosteroids with Placebo as
              Initial Systemic Treatment of Acute GVHD

Protocol: 0802

A. Why am I here?

We are inviting you to join our study because you have acute graft-versus-host disease
(GVHD). We want to learn if a new drug works better than the current drug we use to treat
GHVD.

GVHD happens when your donor cells from your transplant attack parts of the body like
your skin, stomach or liver. Both kids and adults can get GVHD. It can be a very serious
problem for some people.

B. Why are you doing this study?

We are doing this study because we want to learn if a single drug or a combination of drugs
work better to get rid of graft-versus-host disease (GVHD).

- Prednisone with a sugar pill (placebo) or

- Prednisone with MMF (mycophenate mofetil)

C. What will happen to me?

If you say you want to be in the study, we will ask you for several things:

- Permission to let us read your medical records and x-rays.

- Check-ups with the study doctors.

- Some blood from you (about 12 teaspoons). A very small needle will be used to get
  blood.

- We may also need a small piece (biopsy) of your skin, so we can study changes in
  your skin. If you agree to this, we will use numbing medicine before we take a small
  piece of skin with a special tool called a "punch."

Everyone in the study will take prednisone.

You will also take MMF or sugar pills (placebos). The doctors use a computer to choose which one. You will not know which drug you will take. The computer will keep it a secret from everyone, including the study doctors. If you get very sick, your study doctors can find out from the computer which drugs you take.

You will take the MMF or sugar pills 3 times a day for up to 8 weeks. If it is hard to swallow, the doctors can use a small needle to give it through your vein (IV) or your central line.

Once you finish taking the drugs, you will have about 4 more check-ups with either the study doctors or your regular doctor over the next 12 months.

We will watch you carefully for fevers, any sign of infection or other problems.

D. Will it hurt?
When you have your blood taken with a needle, it may feel like a pinch. It will hurt for a minute and sometimes the place where the needle went might be red and sore. You might get a little bruise where the blood was taken but it goes away in a few days.

If you have a skin biopsy, the numbing medicine burns when it goes in, but only for a few seconds. When the numbing medicine wears off, there may be some mild pain. It will leave a small scar.

E. Will the study help me?
We don't know if the study will help you or not. Your GVHD may stay the same, it may get better, or it may get worse.

F. What if I have questions?
You can ask any questions that you have about the study. If you forget to ask a question and think of it later, you can call me [insert office number]. You can also ask your question the next time you see me.

You can call the study office at any time to ask questions about the study.

G. Do I have to be in this study?
If you don't want to be in the study, you need to tell us and your parent or guardian. Your doctor will not be angry or upset if you don't want to join.

Whether you are in the study or not, you will still need to have treatment for your GVHD.

You can say yes now and change your mind at any time.

Please talk this over with your parent or guardian before you decide if you want to be in the study. We will also ask your parents to give their permission for you to join this study.

Use of Blood and DNA Samples
Some of your blood will be used to test for GVHD. Some of your blood and a sample of cells from inside your cheek (DNA) will be saved for future studies. To be in the study, you must agree to have your blood used for GVHD and other regular tests but you do not have to agree to have your blood or cheek cells (DNA) used in future studies.

Please check one of the boxes below to show how you want your blood and cheek cells (DNA) to be used.

❒ Yes, you may use my blood and cheek cell (DNA) samples for this study and future studies of GVHD.

❒ No, you may not use my blood and cheek cell (DNA) samples.

Writing your name on this page means that you agree to be in the study, and know what will happen to you. If you decide to quit the study, all you have to do is tell the person in charge.

You and your parent or guardian will get a copy of this form after you sign it.

_____   _____
Signature of Child   *Date*

_____   _____
Signature of Researcher   *Date*

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

Research Specimens
BMT CTN research samples collected in this protocol will be used for both protocol-defined testing as well as future, undefined research supporting the protocol. All research sample aliquots will be given unique bar code designations that cannot be linked back to the recipient. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the protocol. Samples sent to researchers cannot be linked with any remaining samples at the repository.

Patient samples will be collected both prior to the initiation of treatment and at two post-treatment time points as specified below.

- ➢ Peripheral Blood Sample (Pre-treatment: Day 0) – Whole Blood, Plasma
- ➢ Buccal Swab Samples (Pre-treatment: Day 0) – Patient DNA
- ➢ Peripheral Blood Samples (Post-treatment: Day 28, and 56) –Plasma

Samples processed into frozen cryovial aliquots will be shipped to the BMT CTN Repository on an annual basis in compliance with the shipping procedures specified in the BMT CTN MOP and the 0802 Laboratory Sample Guide.

Biomarker Panel Testing
For these studies, plasma samples collected on Day 0 and Day 28 post-treatment will be shipped from the BMT CTN Repository to the project laboratory and analyzed for a 4-protein biomarker panel. The results from previous discovery and validation studies suggested that the panel of four biomarkers can confirm the diagnosis of aGVHD in patients at onset of clinical symptoms of aGVHD and provide prognostic information independent of aGVHD severity. The plasma protein biomarker panel will include at minimum: interleukin-2-receptor-alpha, tumor-necrosis-factor-receptor-1, interleukin-8, and hepatocyte growth factor (recent data would support the addition of elafin/trappin-2 to this panel). Test panel and project laboratory to be finalized by the Protocol Team as additional on-going study reviews are completed and results discussed with principal investigators. Donor chimerism results recorded at the time nearest to each sample collection will be noted.

Future GVHD Studies
Remaining Day 0 and Day 28 plasma sample aliquots will be stored along with additional Day 56 plasma sample aliquots for future GVHD-related biomarker studies. Additionally, whole blood collected from the patient on Day 0 (representing essentially donor DNA) and buccal swabs for DNA from the patient will be collected, frozen and stored for future GVHD-related biomarker studies.

TABLE C-1: COLLECTION AND SHIPPING PROCEDURES AND COLLECTION SCHEDULE FOR PATIENT BLOOD SAMPLES FOR PROTOCOL-DEFINED BIOMARKER TESTING AND FOR FUTURE, UNDEFINED RESEARCH

TIME POINTS	COLLECTION OF SAMPLE	TYPE OF PROCESSING AND STORAGE	SPECIMEN TO BE SHIPPED	PURPOSE OF SAMPLE	SHIPPING SPECIFICATIONS
Day 0	6 mL peripheral blood (one 6 mL fill EDTA lavender-top tube) Source of Donor DNA	Gently mix one of the 6 ml pre-treatment blood tubes by gently inverting the tube for 60 seconds. Pipette a **1.0 mL** aliquot of the whole blood into each of 6 cryovials and freeze at -70ºC in a scientific grade freezer.	Whole Blood	Future GVHD Studies	Batch ship yearly, frozen on dry ice in a provided shipping container, FedEx priority overnight to the BMT CTN Repository.
	6 mL peripheral blood (one 6 mL fill EDTA lavender-top tube)	Centrifuge the EDTA containing whole blood samples at 1000-1300 x g or 2100 rpm for 10 minutes within 60 minutes of collection. Remove the separated plasma. Transfer **500 µL** aliquots to 4-6 cryovials and freeze at -70ºC in a scientific grade freezer.	Plasma	Future GVHD Studies/4-protein biomarker panel	Batch ship yearly, frozen on dry ice in a provided shipping container, FedEx priority overnight to the BMT CTN Repository.
	4 buccal swabs Source of Patient DNA	Brush swab against the inside of your cheek for approximately 10 seconds. Use the same force used to brush your teeth. Use one swab per section (quadrant) of your cheek. The 4 swabs should be dried for a minimum of **2 hours** before they are processed for long-term frozen storage. Each dried swab is placed into a separate cryovial. Cut the stick so that the cotton swab tip fits well within the cryovial. Secure the cryovial cap and freeze at -70ºC in a scientific grade freezer.	Cheek Swab	Future GVHD Studies	Batch ship yearly, frozen on dry ice in a provided shipping container, FedEx priority overnight to the BMT CTN Repository.
Day 28	10 mL peripheral blood (one 10 mL fill EDTA lavender-top tube)	Centrifuge the EDTA containing whole blood samples at 1000-1300 x g or 2100 rpm for 10 minutes within 60 minutes of collection. Remove the separated plasma. Transfer **500 µL** aliquots to 6-10 cryovials and freeze at -70ºC in a scientific grade freezer.	Plasma	Future GVHD Studies/4-protein biomarker	Batch ship yearly, frozen on dry ice in a provided shipping container, FedEx priority overnight to the BMT CTN Repository.

TIME POINTS	COLLECTION OF SAMPLE	TYPE OF PROCESSING AND STORAGE	SPECIMEN TO BE SHIPPED	PURPOSE OF SAMPLE	SHIPPING SPECIFICATIONS
Day 56	10 mL peripheral blood (one 10 mL fill EDTA lavender-top tube)	Centrifuge the EDTA containing whole blood samples at 1000-1300 x g or 2100 rpm for 10 minutes within 60 minutes of collection. Remove the separated plasma. Transfer **500 µL** aliquots to 6-10 cryovials and freeze at -70ºC in a scientific grade freezer.	Plasma	Future GVHD Studies	Batch ship yearly, frozen on dry ice in a provided shipping container, FedEx priority overnight to the BMT CTN Repository.

APPENDIX D

DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

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DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

Background – The Sequential Probability Ratio Test

Let $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0 : \theta = \theta_o$ versus $H_1 : \theta = \theta_1$ decides in favor of H_1 or H_0 if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i f(x_i;\theta_1) / f(x_i;\theta_0)$ is the likelihood ratio, and c_α is determined to have the size α. When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B < L_n < A$ for some constant $B < 1 < A$, stops sampling and decides in favor of H_1 as soon as $L_n > A$, and stops sampling and decides in favor of H_0 as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$, and of accepting H_0 when $\theta = \theta_1$, respectively, and the expected sample size $E(N | \theta_j) \equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0) \leq \alpha$ and $\Pr_1(\text{reject } H_0) \leq \beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2,...$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1(> \theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities α and β, the SPRT boundaries are given approximately by $A = (1 - \beta)/\alpha$ and $B = \beta/(1 - \alpha)$. The operating characteristics of the SPRT are given by $O(\theta, \alpha, \beta, \theta_0, \theta_1) = (A^{h(\theta)} - 1)/(A^{h(\theta)} - B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int (f(x;\theta_1) / f(x,\theta_2))^{h(\theta)} f(x;\theta)dx = 1$.

The formula $E(N;\theta) = [[(1 - O(\theta)]\log A + O(\theta) \log B]/ E(z;\theta)$ provides the average sample number for an arbitrary θ. The sample size distribution is very highly skewed, $Var(N) \approx [E(N)]^2$. Thus we will consider a truncated test with maximum sample size of N_0 and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Uncensored Exponential Survival Times

For example, we wish to construct a sequential test for the composite null hypothesis that the rate of treatment-related mortality (TRM) at 100 days is less than or equal to 30% versus the alternative hypothesis that it is greater than or equal to 50%. For the derivation of the uncensored SPRT, we will require that the type I error of the test be less than 5%, and that the test provide 80% power to reject the null hypothesis under a specified alternative that the true rate is 50%. A maximum sample size of 50 patients will be permitted.

Let us assume that the survival times, $T_1, T_2, ..., T_n$, are completely observed (uncensored) and are i.i.d. with exponential density function $f(T, \theta) = \theta e^{-\theta T}$. These assumptions will be relaxed to incompletely observed data subsequently. In the exponential parameterization, a 100-day survival rate of 70% translates into a mean survival of 0.768 years ($\theta_0 = 1.303$), and 50% translates into a mean survival of 0.395 years ($\theta_1 = 2.532$).

The SPRT is derived with reference to a simple null and alternative hypothesis, in this case, $H_0 : \theta = \theta_o = 1.303$ versus $H_1 : \theta = \theta_1 = 2.532$. However, since the log-likelihood ratio for the exponential, $\log \prod_i^n f(x_i; \theta_1) - \log \prod_i^n f(x_i, \theta_0) = n(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, is a monotone function of $\sum_i^n T_i$, the power of the test is non-decreasing in θ. Thus the SPRT is a one-sided level .05 test of a composite null ($H_0 : \theta \leq \theta_o = 1.303$) versus a composite alternative ($H_1 : \theta \geq \theta_o = 1.303$), with power of $1 - \beta = .80$ at the selected alternative $\theta = \theta_1 = 2.532$.

The SPRT can be represented graphically. The continuation region is bounded by two parallel lines with common slope $(\log \theta_0 - \log \theta_1)/(\theta_0 - \theta_1) = 0.541$, and intercepts $\log A /(\theta_0 - \theta_1) = -2.256$ and $\log B /(\theta_0 - \theta_1) = 1.270$, for the lower and upper bounds, respectively. As each individual unit is put on trial and observed to fail, the cumulative sum of failure times, $\sum_i^n T_i$, is recomputed, and plotted against the current sample size, n. When this graph crosses the lower boundary, the null hypothesis is rejected.

The maximum sample size of 50 patients requires that the SPRT be truncated. We choose to truncate the SPRT by declaring that if the test has failed to terminate after 50 patients, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at a sample size of 50 is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity.

Derivation of a Modified SPRT for Censored Exponential Data

The assumption of uncensored exponential survival times is flawed. However, we consider it reasonable to assume the hazard for TRM is constant over the first 100 days post-transplant, and we will restrict our attention to this time interval. Furthermore, it is not practical to conduct a clinical study by putting each individual on trial, and waiting until that individual is observed to fail. We relax our assumptions as follows. Firstly, each individual's time on study will be computed as time from transplant to failure, or to the 100 day time point, whichever comes first. Secondly, we will put individuals on trial as soon as they become available, without waiting for the previous individual to fail.

Let us consider the impact of relaxing these assumptions one at a time. In a fixed sample size trial with uncensored exponential failure times, mean survival time is estimated by the sample mean of the failure times, or total time on study divided by the number of individuals enrolled. When censoring is introduced, the estimate becomes the total time on study divided by the number of observed (non-censored) failures. This suggests that in an exponential SPRT test modified to incorporate censoring, we replace the observed failure times, $T_1, T_2,..., T_n$, with censored failures times, $x_1, x_2,..., x_n$, and the current sample size, n, with the number of observed failures, d.

Now we relax the second assumption, and put individuals on trial as soon as they become available, without waiting for the previous individual to fail. Assume that three years are required for accrual of 50 patients to the study, and that the final analysis takes place 100 days after the last patient is entered. Putting all of this together, we propose a modified truncated SPRT, where at any interim time point, s, ranging from 0 to 3 years 100 days, the sum of observed time on study, $\sum_{i}^{n} X_i(s)$ is plotted against the number of observed failures, $d(s)$. In practice, monitoring will be scheduled monthly after the start of enrollment to the study. A further modification to the SPRT was to only use the lower boundary for stopping since the primary focus of the monitoring is to protect against unacceptable 100-day TRM rates.

Operating Characteristics of the Modified SPRT Test for Censored Exponential Data

Recall that the uncensored SPRT targeted a drop in survival at Day 100 from 70% to 50%, with type I and II errors of 5% and 20%. Since only the lower boundary is used for monitoring, the continuation region of the test was bounded below by a line with a slope of 0.541 and intercept of –2.256. The effect of truncation is to reduce the power of the test. In order to compensate for this, we raise the lower boundary to make it easier to cross. Under the further assumption of uniform accrual over a three year period, and monthly interim analyses over the course of the study, the operating characteristics of the modified SPRT were obtained from a simulation study. These simulation show that an intercept of –1.741, corresponding to setting parameters α and β to 10% and 15%, result in empirical type I and II error rates of about 5% and 20%.

**Table D-1   Operating Characteristics of Sequential Testing Procedures from a
Simulation Study with 100,000 Replications**

Treatment-Related Mortality (TRM)

True 100-Day Rate	30%	35%	40%	45%	50%
Probability Reject Null	0.07	0.20	0.41	0.66	0.86
Mean Month Stopped	34.5	32.3	28.5	23.5	18.5
Mean # Endpoints in 100 Days	13.8	15.0	15.1	14.0	12.1
Mean # Patients Enrolled	48	45	40	33	26

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true rate of TRM on or before Day 100 was 30%, the test crossed the lower boundary in 7119 of 100,000 replications, for an estimated type I error rate of 7%. When the true rate of TRM on or before Day 100 was 50%, the test failed to cross the boundary in 14226 of 100,000 replications, for an estimated type II error rate of 14%. And on average, the boundary will be crossed at 18.5 months, when 26 patients will be enrolled to the study.

It is interesting to note that the SPRT derived above for exponential failure times with censoring at 100 days, has operating characteristics which are similar to those of a more traditional SPRT, derived for binomial variates with success probability equal to the 100 day failure rate. Using time to failure rather than a simple binary indicator of failure, leads to little improvement in power when failure times are censored relatively soon after entry on study. We speculate that if the constant hazard rate over the first 100 days were high, the exponential test would reject faster than the binomial test, but have not conducted simulation studies to demonstrate this.

APPENDIX E

M.D. ANDERSON SYMPTOM INVENTORY (MDASI)
CORE ITEMS

Date: _____   Institution:_____

Subject Initials: _____   Hospital Chart #:_____

Study Subject #: _____

M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours.* Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	As Bad As You Can Imagine 9	10
1. Your **pain** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
2. Your **fatigue (tiredness)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
3. Your **nausea** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
4. Your **disturbed sleep** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
5. Your **feelings of being distressed (upset)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
6. Your **shortness of breath** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
7. Your **problem with remembering things** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
8. Your **problem with lack of appetite** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
9. Your **feeling drowsy (sleepy)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
10. Your having a **dry mouth** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Date: _____

Institution: _____

Subject Initials: _____

Hospital Chart #: _____

Study Subject #: _____

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
11. Your feeling sad at its WORST?	O	O	O	O	O	O	O	O	O	O	O
12. Your vomiting at its WORST?	O	O	O	O	O	O	O	O	O	O	O
13. Your numbness or tingling at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interefered Completely
	0	1	2	3	4	5	6	7	8	9	10
14. General activity?	O	O	O	O	O	O	O	O	O	O	O
15. Mood?	O	O	O	O	O	O	O	O	O	O	O
16. Work (including work around the house)?	O	O	O	O	O	O	O	O	O	O	O
17. Relations with other people?	O	O	O	O	O	O	O	O	O	O	O
18. Walking?	O	O	O	O	O	O	O	O	O	O	O
19. Enjoyment of life?	O	O	O	O	O	O	O	O	O	O	O

APPENDIX F

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APPENDIX F

REFERENCES

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