
# 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


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# 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 Historical published and unpublished data from Johns Hopkins, M. D. Anderson, University of Michigan and others defined an expected 35%-53% complete response (CR) at Day +28 of corticosteroid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.<br>2. Acute GVHD developing after pre-planned DLI is eligible.<br>3. Grade I-IV acute GVHD requiring systemic therapy.<br>4. Patients of all ages will be included.<br>5. Biopsy confirmation of GVHD is recommended, but not required. Enrollment should not be delayed awaiting biopsy or pathology results.<br>*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<br>*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<br>8. ANC greater than 500/μL.<br>9. Signed informed consent and/or assent.<br>10. Assent and educational materials provided to, and reviewed with, patients under the age of 18. | 1. Mycophenolate mofetil or mycophenolic acid (Myfortic) given within 7 days of enrollment.<br>2. Active uncontrolled infection.<br>3. Relapsed/persistent malignancy requiring rapid immune suppression withdrawal.<br>4. Patients that have undergone an unscheduled (or not part of original transplant therapy plan) DLI.<br>5. Patients unlikely to be available at the transplant center on Day 28 and 56 of therapy.<br>6. A clinical syndrome resembling de novo chronic GVHD developing at any time after BMT.<br>7. Other drugs for GVHD treatment<br>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.<br>9. Patients who are pregnant, breast feeding, or if sexually active, unwilling to use effective birth control for the duration of the study.<br>10. Adults unable to provide informed consent<br>11. Patient on dialysis.<br>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.<br>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.

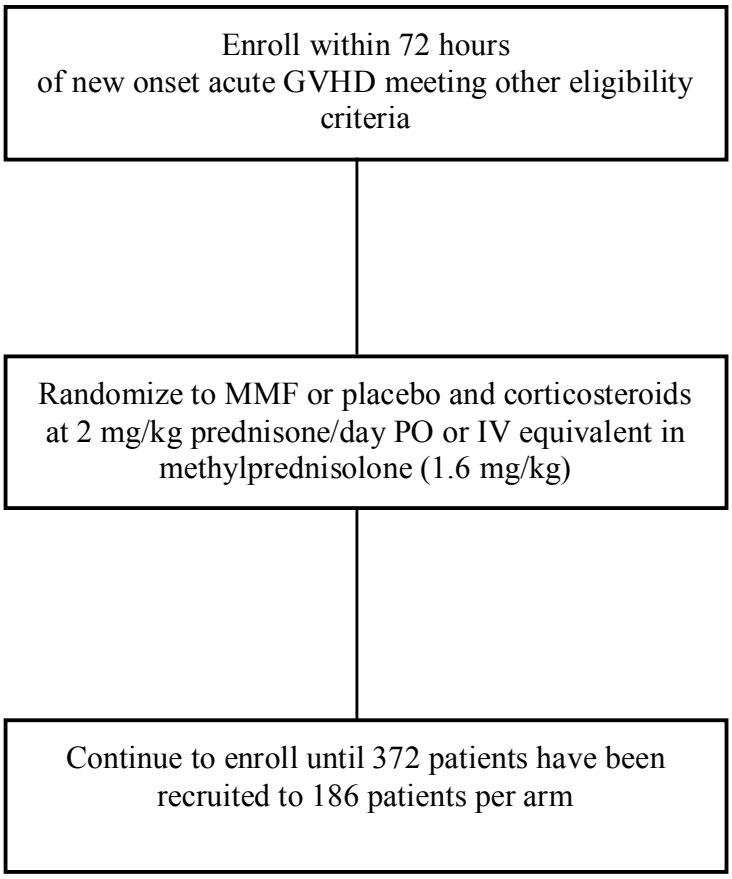
If acute GVHD progresses within 5 days or no response within 14 days, then treat with alternative systemic secondary GVHD therapy at the physician's discretion. This patient would be considered a failure for the primary endpoint. This patient will be considered "off study treatment", but will remain 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):**<br>2 mg/kg/day once or twice a day Days 1-5.<br>1.5 mg/kg/day once daily Days 6-10.<br>1 mg/kg/day Days 11-15.<br>0.5 mg/kg/day Days 16-20<br>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 $\leq$ 0.2 mg/per/kg per day of prednisone or $\leq$ 0.16 mg/per/kg per day of methylprednisolone by Day 56. | **Primary endpoint:**<br>- Acute and chronic GVHD free survival at Day 56 after randomization.<br>**Secondary endpoints:**<br>- Proportion of CR, PR, mixed response, no response and progression, among surviving patients at Days 14, 28 and 56.<br>- Treatment failure (defined as no response, progression, administration of additional therapy fro GVHD, or mortality) at Days 14, 28, and 56.<br>- 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.<br>- Incidence of discontinuation of immune suppression without acute GVHD flare and without disease progression/recurrence by Days 56, 180, and 360 post-therapy.<br>- Steroid dose at Day 28 and Day 56.<br>- Incidence of topical/non absorbable therapy at Day 56.<br>- Incidence of Chronic GVHD by 6 and 12 months.<br>- Overall and GVHD free survival at 6 and 12 months after randomization.<br>- Incidence of systemic infections within 6 months of therapy.<br>- Incidence of EBV PTLD or EBV reactivation requiring therapy.<br>- Disease-free survival at 6 and 12 months post randomization.<br>- Non-relapse mortality at 6 and 12 months post randomization.<br>- Change in patient-reported outcomes from enrollment to Day 56. |

# STUDY DESIGN SCHEMATIC




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).

### 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)

### 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]