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 Historical published and unpublished data from Johns Hopkins, M. D. Anderson, University of Michigan and others defined an expected 35%-53% complete response (CR) at Day +28 of corticosteroid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

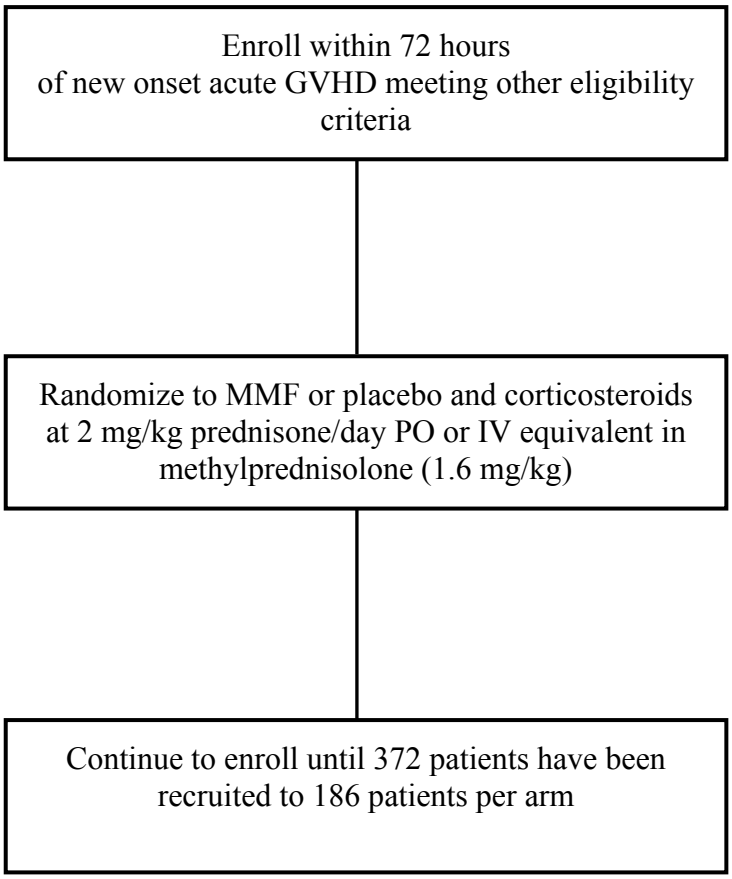
If acute GVHD progresses within 5 days or no response within 14 days, then treat with alternative systemic secondary GVHD therapy at the physician's discretion. This patient would be considered a failure for the primary endpoint. This patient will be considered "off study treatment", but will remain 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 $\leq$ 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:** - 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



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.