# PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 0302

## Initial Systemic Treatment of Acute GVHD: A Phase II Randomized Trial Evaluating Etanercept, Mycophenolate Mofetil (MMF), Denileukin Diftitox (ONTAK) and Pentostatin in Addition to Corticosteroids

**Principal Investigator:** Daniel Weisdorf, M.D.

**Study Design:** The study is a randomized Phase II, four arm treatment trial. The primary purpose of the study is to define new agents with promising activity against acute GVHD suitable for testing against corticosteroids alone in a subsequent Phase III trial.

Corticosteroids have been used as primary therapy for acute GVHD for many years. Historical published and unpublished data from the University of Minnesota, Dana Farber Cancer Institute and the Fred Hutchinson Cancer Center define an expected 35% complete response (CR) at Day +28 of corticosteroid therapy for previously untreated patients with acute GVHD.

In this trial, patients with newly diagnosed acute GVHD will receive corticosteroids plus one of four new agents. A control arm of only corticosteroids will not be employed. Each agent will be assessed for safety (stopping rules defined) and efficacy (≥ 35% CR rate at Day 28 of therapy).

**Primary Objective:** The primary objective is to estimate the proportion of CR at Day 28 of therapy for newly diagnosed acute GVHD for each of these agents given in combination with corticosteroids.

**Secondary Objectives:** Secondary objectives are to determine: proportion of partial response (PR), mixed response and progression at Day 28; proportion of treatment failure (no response, progression, administration of additional therapy for GVHD, or mortality) by Day 14; the incidence of GVHD flares requiring increasing therapy before Day 90. In addition, the following endpoints will be examined: incidence of discontinuation of immune suppression without flare by Days 90, 180 and 270 post-therapy, incidence of chronic GVHD by 9 months, overall survival at 6 and 9 months post initiation of therapy, incidence of systemic infections within 3 months of initiation of therapy, incidence of EBV-associated lymphoma**.**

**Eligibility:** Patients must be greater than or equal to 6 years of age and have acute GVHD requiring systemic therapy. No previous systemic immune suppressive therapy for acute GVHD is allowed except for a maximum 48 hours of prior corticosteroid therapy (≥ 1 mg/kg/day methylprednisolone). Patients receiving ONTAK, pentostatin, or etanercept within 7 days of screening will be excluded. Patients receiving MMF for GVHD prophylaxis will be randomized into one of the other three treatment arms. Patients must have an absolute neutrophil

count (ANC) greater than 500/μL and an estimated creatinine clearance greater than 30 mL/minute.

**Treatment Description:** The treatment schedules are as follows: **Etanercept** [25 mg subcutaneously twice weekly for up to 4 weeks; discontinue if in CR by 4 weeks]. Mycophenolate mofetil (**MMF)** [20 mg/kg (maximum 1 gm) PO or IV BID; continue through prednisone taper, then taper MMF over 4 weeks]. Denileukin Diftitox (**ONTAK®)** [9 mcg/kg IV Days 1, 3, 5, 15, 17, 19]. **Pentostatin** [1.5 mg/m$^2$ daily for 3 days; Days 1-3 and repeat Days 15-17].

All patients will receive methylprednisolone 2 mg/kg/day IV (or prednisone 2.5 mg/kg/day PO) divided in 2-3 daily doses for at least 7 days. Prednisone may be tapered as tolerated to no less than 0.75 mg/kg/day (methylprednisolone 0.6 mg/kg/day) at Day 28 of therapy. If not in CR at Day 28, patients will be followed for study endpoints, but assigned therapy can be continued or changed per institutional guidelines.

In addition to prescribed study drug plus corticosteroids, all patients should receive transfusion support per institutional practice; anti-infective prophylaxis directed towards CMV, gram positive (encapsulated) bacteria, pneumocystis carinii and fungal infections

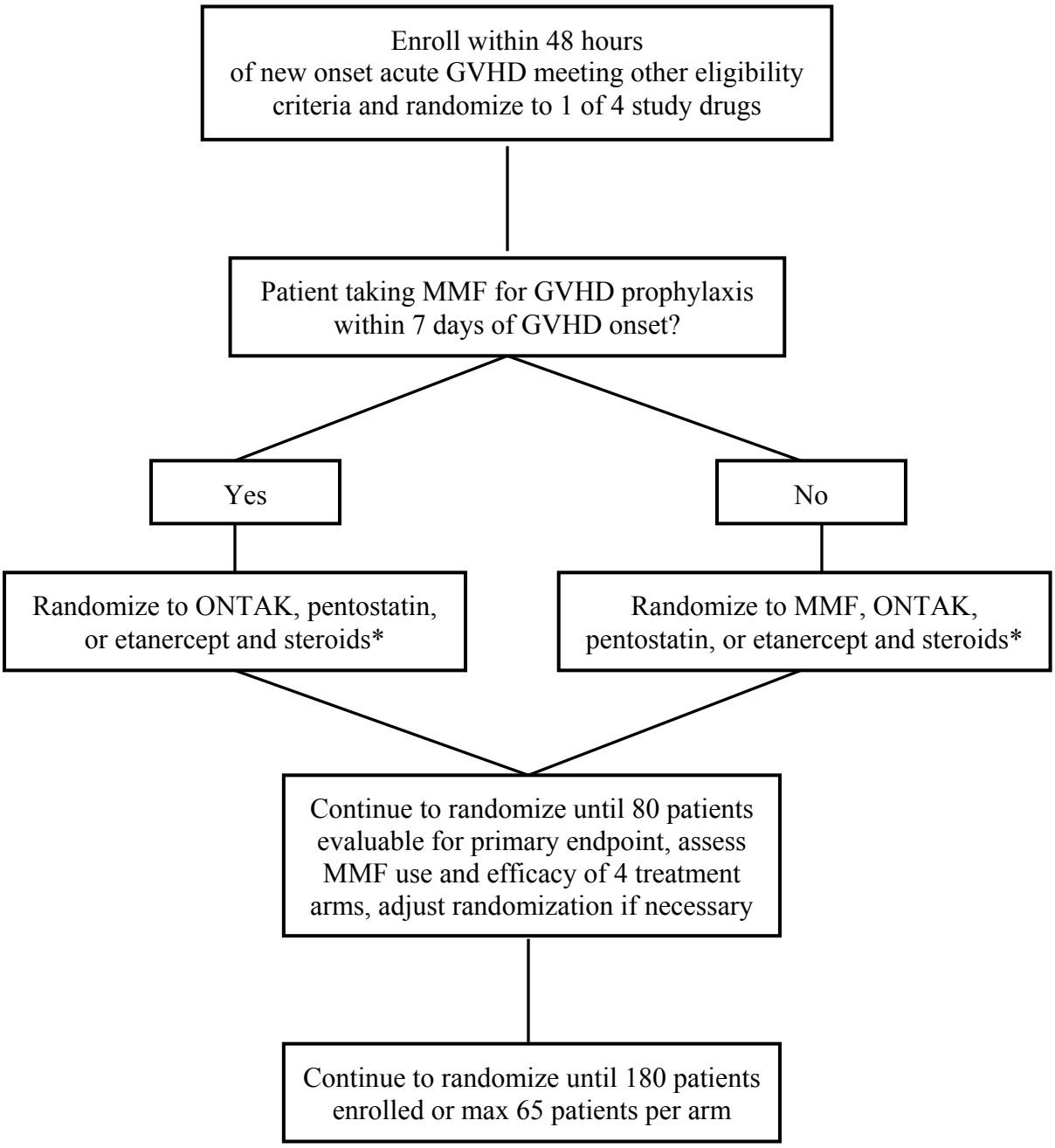
Weekly GVHD organ stage scores, overall clinical grade, biopsy information for GVHD and relevant differential diagnosis will be recorded and reported to the BMT CTN Data Coordinating Center (DCC).

**Accrual Objective:** A maximum of 180 patients, but at most 65 per arm, will be randomized to one of the four treatment arms. After 80 patients are evaluable for the primary endpoint, if in any experimental arm, observed responses suggest a posterior probability > 85% that an arm will have a true CR < 35%, enrollment to the arm will cease and the arm will be excluded from further consideration due to lack of evidence for efficacy.

**Accrual Period:** The estimated accrual period is 12 months.

**Study Duration:** Patients will be followed for 9 months following initiation of therapy.

# STUDY DESIGN SCHEMATIC




* Steroids = 2.5 mg/kg prednisone/day PO or IV equivalent in methylprednisolone (2 mg/kg) divided 2-3 times daily

Primary Endpoint:
Proportion of CR at Day 28 of therapy.

# STUDY SCHEMA

**Aim:** To determine if any of four new agents, given in addition to corticosteroids as initial therapy for acute GVHD improves response rate and overall clinical outcome.

| **Inclusion Criteria** | **Exclusion Criteria** |
|---|---|
| 1. Prior allogeneic hematopoietic stem cell transplant using either bone marrow, PBSC or cord blood.<br>2. De novo acute GVHD diagnosed **within 48 hours** prior to enrollment. Biopsy confirmation of GVHD is strongly recommended but not required. Enrollment should not be delayed awaiting biopsy or pathology results. The patient must have had no previous systemic immune suppressive therapy given for treatment of acute GVHD except for a maximum 48 hours of prior corticosteroid therapy (≥ 1 mg/kg/day methylprednisolone).<br>3. GVHD developing following DLI for prophylaxis or planned DLI.<br>4. ≥ 6 years of age at enrollment.<br>5. Clinical status at enrollment to allow tapering of steroids to not less than 0.6 mg/kg/day methylprednisolone (0.75 mg/kg/day prednisone) at Day 28 of therapy (e.g. persisting malignant disease suggesting the need for accelerated taper of immunosuppression).<br>6. ANC greater than 500/μL.<br>7. Estimated creatinine clearance greater than 30 mL/minute<br>8. Signed informed consent and/or assent.<br>9. Assent and educational materials provided to, and reviewed with, patients under the age of 18. | 1. ONTAK, pentostatin or etanercept given within 7 days of enrollment.<br>2. Isolated limited skin GVHD as the sole manifestation of acute GVHD.<br>3. Active uncontrolled infection.<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 allotransplantation.<br>7. Other investigational therapeutics for GVHD within 30 days, including agents used for GVHD prophylaxis.<br>8. If any prior steroid therapy (for indication other than GVHD), treatment at doses > 0.5 mg/kg/d 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. Patients with a history of intolerance to any of the study drugs. |

**If any improvement after 7 days of full dose corticosteroids + study drug**: Taper steroids as tolerated to no less than 0.75 mg/kg/day prednisone (or 0.6 mg/kg/day methylprednisolone) on Day 28. 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.

**Suggested prednisone taper for responders (round to nearest 5 mg of prednisone):**
2.5 mg/kg/day divided in 2-3 doses Day 0-6
2.5 mg/kg/day once daily Day 7-13
2 mg/kg/day Day 14-21
1.4 mg/kg/day Day 21-28
0.75 mg/kg/day Day 29-35
0.6 mg/kg/day Day 36-42
0.4 mg/kg/day Day 43-49
0.25 mg/kg/day Day 50-56
0.1 mg/kg/day Day 57-63
0.1 mg/kg every other day, Day 63-69;
Discontinue on Day 70

**Primary endpoint:**
Proportion of CR at Day 28 of therapy

**Secondary endpoints:**
- Proportion of PR, mixed response and progression at Day 28
- Proportion of NR, progression, administration of additional therapy for GVHD, or mortality by Day 14
- Incidence of GVHD flares requiring increasing therapy before Day 90
- Incidence of discontinuing immune suppression without flare by Day 90, 180 and 270 post therapy
- Incidence of Chronic GVHD by 9 months
- Survival at 6 and 9 months after initiation of treatment
- Incidence of systemic infections within 3 months of therapy
- Incidence of EBV lymphoma within 9 months of therapy

If acute GVHD progresses within 7 days or no response within 14 days, then treat with alternative secondary GVHD therapy off study, but follow for study endpoints.