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

Changes to Protocol from Version 2.0 to Version 3.0

Additions are noted in underlined text; deletions are noted in strike-out text

§2.3.1.4 Inclusion Criteria: 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 *after* the onset of acute GVHD.

§2.4.3 MMF/Placebo Formulation, Dosing and Duration:

- *Formulation and Drug Supply*:
  - Oral MMF/placebo is available as 250 mg capsules in bottles of ~~100~~ 70 each.
  - The dose preparation instructions were modified: Dilute 1-g doses in 140 mL D5W ~~1.5-g doses into 210 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.
  - At the completion of the study, unused MMF/Placebo study drug should be returned to the study team by the patient for destruction ~~and the Pharmacy will issue a Destruction Form~~ as per institutional practice of the Investigational Pharmacy. ~~Unused study drug supply will be returned to BMT CTN/EMMES~~.
- *Dose and Administration*:
  - The study drug capsule may not be opened to administer.
  - Patients who weigh <40 kg should receive 20 mg/kg IV or PO (up to 750 mg) every 8 hours.
  - Patients with 500 ≤ ANC < 1000 at time of enrollment should receive study drug every 12 hours. Once ANC ≥ 1000 q8 hour dosing should be instituted.

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

§2.9 Supportive Care Guidelines: CMV monitoring guidelines were modified: ~~Pre-emptive monitoring and treatment strategy for CMV is strongly recommended.~~ 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.

§3.2.5 ~~Cumulative~~ Steroid Dose at Days 28 and 56 after Randomization and Protocol Synopsis, Secondary Objectives: 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 and Day 56 will be recorded…~~during this interval.~~

§3.2.13 Change in Patient-reported Outcomes from Enrollment to Day 56: ~~Adult patients (older than 18 years of age) will complete a quality of life questionnaire~~. 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....

§4.1 Enrollment and Randomization:

- #1. An authorized user at the clinical center completes the initial screening … within 72 hours of need of systemic therapy for acute GVHD.
- #3. A visit schedule based on ~~treatment start~~ enrollment date is displayed for printing.

§4.1.1 Randomization: Patients will be randomized within 72 hours of ~~diagnosis/~~need of systemic therapy of acute GVHD.

Table 4.2.1: Target day range = ±3 days ~~up to Week 8~~ for Day 7 (subsequent visits through Day 56 must be scheduled weekly)…

Table 4.2.1, §4.2.2 Assessments, and Table 4.2.2: 4 months was removed as a post-randomization time point.

Table 4.2.2: *+/- 3 days to allow for scheduling flexibility, holidays, etc. Subsequent visits through Day 56 must be scheduled weekly

§4.2.4: Serious Adverse Event (SAE) Reporting: The section was replaced with the following text: 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.

§4.2.5 Study Drug Dose Reduction Monitoring: 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 ~~to BID~~ in the MMF and placebo arms by Day 28. Sustained dose reduction will be defined as reduction from TID ~~to BID~~ dosing for reasons of toxicity for the duration of at least 1 week without re-escalation of dose.

§5.3.5 Monitoring Guidelines for Dose Reduction: The definition of dose reduction was clarified: Dose reduction is defined as one week of sustained ~~dose <3 mg daily~~ dose reduction from TID dosing through Day 28.

§5.5.5 ~~Cumulative~~ Steroid Dose at Days 28 and 56 after Randomization: The median and range of ~~cumulative~~ steroid doses at each time point will be provided separately for each treatment group. The median ~~cumulative~~ steroid dose will be compared between treatment groups using the Wilcoxon rank sum test.

§Appendix C, Laboratory Procedures (see attached revised Table C-1):

- Table C-1 has been revised to sort research specimens by collection day, as summarized below:
  - Day 0: 6ml whole blood (Future GVHD studies), 6ml plasma (Future GVHD studies/4-protein biomarker panel), 4 buccal swabs (Future GVHD studies)

- Day 28: 10 ml plasma (Future GVHD studies/4-protein biomarker panel)
- Day 56: 10 ml plasma (Future GVHD studies)

- The centrifuge speed was corrected: Centrifuge the EDTA containing whole blood samples at ~~100~~ 1000 -1300 x g or 2100 rpm for 10 minutes within 60 minutes of collection.

Changes to Appendix B, Informed Consent, from Version 2.0 to Version 3.0

§Introduction: 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.

§Procedures, Monthly Health Evaluations: Once you finish the 8 weeks of study treatment, we will evaluate you at approximately 3, ~~4,~~ 6 and 12 months after you first joined the study.

§Risks and Discomforts (b) Infections: There is a higher risk of infection in patients with GVHD.... Infections may be bad enough to cause death.

§Blood and DNA Samples for Research: The following four paragraphs were added to the Blood and DNA Samples for Research section:

- 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.

§Blood and DNA Samples for Research, Procedures: The fourth bullet was corrected: "These samples may be stored ~~up to 10 years~~ indefinitely for future research ~~studies on GVHD".~~

Changes to Appendix B, Assent, from Version 2.0 to Version 3.0

§ C. What will happen to me?: You will take the MMF or sugar pills 3 times a day for up to 8 weeks. ~~They can be pills or liquid.~~ If it is hard to swallow, the doctors can use a small needle to give it through your vein (IV) or your central line.

REVISED 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.