BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PROTOCOL #1501 Standard-risk acute GVHD

A Randomized, Phase II, Multicenter, Open Label, Study Evaluating Sirolimus and Prednisone in Patients with Refined Minnesota Standard Risk, Ann Arbor 1/2 Confirmed Acute Graft-Versus-Host Disease

FREQUENTLY ASKED QUESTIONS (FAQs)

1. Why is a study evaluating a non-steroid therapy for acute GVHD?

Corticosteroids have served as the primary therapy for acute GVHD for several decades. Acute GVHD treatment with single-agent corticosteroid therapy has modest efficacy and is associated with significant morbidity. Therefore, new steroid-free strategies that control GVHD with little toxicity are needed.

2. Why is the study limited to only standard-risk (SR) acute GVHD patients?

The Refined Minnesota Criteria classifies newly diagnosed acute GVHD into two groups: (i) standard-risk (SR) acute GVHD and (ii) high-risk (HR) acute GVHD, based on patient's clinical presentation. With steroid-based treatments the SR acute GVHD patients have a day 28 complete remission (CR)/partial remissions (PR) rate of 69% (as opposed to 43% for HR patients) and 6 month treatment related mortality (TRM) of 22% (as opposed to 44% in HR patients). By restricting eligibility to SR acute GVHD, BMT CTN 1501 aims to evaluate steroid-free GVHD therapy only in the cohort of lower-risk patients, while simultaneously avoiding therapy de-escalation in the HR acute GVHD patients, with poor prognosis.

3. Will assigning SR acute GVHD designation to newly diagnosed GVHD patients be difficult for the participating centers?

The Refined Minnesota Criteria is simple to use, intuitive and based on routinely available clinical information used to grade acute GVHD. In addition the participating centers will have access to an easy-to-use, free, public webpage (http://z.umn.edu/MNAcuteGVHDRiskScore) which makes the process of assigning risk-category to an individual patient simple and error-free. The website is compatible with all hand-held devices and smart phones, and the process requires <60 seconds.

4. Why is this study using Biomarkers to risk stratify patients in addition to clinical criteria (i.e. the Refined Minnesota Criteria)?

The University of Michigan group has developed a biomarker risk score that classifies newly diagnosed acute GVHD patients into three groups: Ann Arbor 1 (AA1) low-risk acute GVHD, AA2 intermediate-risk acute GVHD, and AA3 high-risk acute GVHD. The high-risk AA3 patients have poor outcomes with day 28 CR/PR rate of 46% and 6 month TRM of >40%. Unpublished data show that among patients with SR acute GVHD (as defined by the clinical Refined Minnesota Criteria), approximately 15-20% have high-risk AA3 disease. These observations signify that classifying acute GVHD solely by clinical criteria can lead to *lower-risk* designation to ~20% patients that have high-risk disease by biomarker assays. Applying standard-risk designation in BMT CTN 1501 study, by using both clinical criteria and biomarker assay (AA1 & AA2) will ensure that clinical investigation of steroid sparing acute GVHD therapies is restricted only to patients with low-risk disease.

5. How will be the biomarker specimen processed and results communicated to the centers?

After confirming eligibility, acute GVHD patients will be randomized in a 1:1 fashion to receive either sirolimus or prednisone. In addition, for biomarker analysis a peripheral blood specimen will be shipped priority overnight to a CLIA certified laboratory at Mount Sinai Medical School. Samples can be shipped Monday to Friday, and results can be delivered Tuesday through Saturday. After confirming the Ann Arbor score, the investigator at the participating center will be notified if the patient has AA1/2, AA3 or missing biomarker risk status by telephone with email written confirmation. Treating physicians will be notified of the patient's Ann Arbor GVHD score within 72 hours of study enrollment (usually within 48 hours).

6. Why would there be a missing biomarker status?

Patients will have a single vial of blood drawn and shipped to the Mount Sinai Medical School laboratory for biomarker panel analysis to determine if they are Ann Arbor 1, 2 or 3. In the event that a shipment is lost, the vial of blood is broken or an error with the assay occurred, a patient would not have a biomarker Ann Arbor score result. If this is the case, their results would be listed as missing, and the patient may continue on their randomized treatment or change their treatment, at the discretion of the treating physician.

7. Why was sirolimus chosen as the steroid sparing approach for this trial?

Steroid sparing therapies for lower-risk acute GVHD is an unmet medical need. The investigators at the Moffitt Cancer Center evaluated single-agent sirolimus as the primary therapy of new onset acute GVHD in 32 allogeneic transplant recipients. Twenty-seven patients (84%) had SR acute GVHD and 5 (16%) were HR. Sirolimus was administered orally at a

median loading dose of 6mg (range 2 to 9 mg), followed by maintenance dosing to sustain the desired target therapeutic levels (5-14ng/mL).

- Sixteen (50%) patients achieved CR of acute GVHD (defined as sustained complete resolution GVHD for 4 weeks without addition of prednisone or other systemic immune suppressive agents) following primary therapy with sirolimus.
- Among the 27 SR acute GVHD patients included in this study, the day 28 CR/PR rate was 56% (95% CI=37-74%).
- No unexpected and/or severe toxicities with this approach were seen.

These results support the use of sirolimus as the steroid sparing acute GVHD treatment in patients with SR acute GVHD.

8. Will the participating centers have experience with sirolimus use and therapeutic level monitoring?

Sirolimus is commonly used either as a standard-of-care prophylactic agent against acute GVHD or as treatment of acute or chronic GVHD. The BMT CTN 1501 protocol provides guidelines on sirolimus use and therapeutic level monitoring. In a survey of BMT CTN Core and Affiliate Centers, all responders indicated prior center experience with using sirolimus as a therapeutic or prophylactic agent for GVHD. In addition, the majority of centers indicated in-house capability of measuring sirolimus levels, while the minority of centers not performing these levels in-house had mechanisms already in place for obtaining these levels in a reference laboratory.

9. Why is the study using 2mg/kg prednisone (or equivalent) as starting dose in all patients with SR acute GVHD?

The starting dose of prednisone at 2mg/kg (or equivalent) in the control arm of BMT CTN 1501 study was selected after careful consideration.

- The study is limited to patients with standard-risk acute GVHD according to the Refined Minnesota Risk Criteria. The primary analysis will only look at patients with AA1 or AA2 biomarker status. Acute GVHD risk-stratification in either the clinical or biomarker-based systems was developed in a cohort of patients receiving frontline therapy with 2mg/kg of prednisone (or equivalent).
- 2mg/kg prednisone was the starting steroid dose used in BMT CTN 0302 and 0802 studies that included ~80% of patients with SR acute GVHD.
- The starting 2mg/kg prednisone dose will be required only for the first 3 days on the protocol (in line with BMT CTN 0802 study), following which treating physicians can choose to taper per their institutional standards. The flexibility in the prednisone tapering schedule, following the first three days serves to ensure that the steroid therapy in the control arm is reflective of real-world practice.

10. Why is a steroid tapering schedule provided in the protocol?

The protocol provides a *suggested* (but not mandated) steroid tapering schedule. This tapering schedule will serve as a roadmap for participating centers, guiding how to achieve a target prednisone dose of ≤0.25mg/kg by day 28 (a secondary endpoint of the protocol).

11. What is the justification for the primary endpoint and the many secondary endpoints?

The primary endpoint is the rate of CR/PR on day 28 post-randomization, without the need of further therapy in both arms. The study has adopted the day 28 responses for primary endpoint, as acute GVHD response rates at this time point have previously been validated to predict rates of later TRM (MacMillan M et al. Blood 2010 & Saliba RM et al. Bone Marrow Transplant 2012). Besides obtaining information on response rates, it is very important to review other safety and efficacy parameters (the secondary endpoints).

12. Why isn't there a time constraint from the need to systemic therapy to enrollment?

Several factors were considered: First, GVHD onset time can be ambiguous, as – prior to the treating clinician's judgment that GVHD is present – there can be a period of several competing potential explanations for the findings and diagnostic work-up to confirm the diagnosis. In this setting, it is difficult to exactly pinpoint the time of onset. As this may not be documented in the medical record, it makes source verification of GVHD onset time difficult. Second, GVHD may be relatively low grade at onset (e.g., minimal findings not treated at all, or minor findings amenable to topical therapies only), and rather only require systemic therapy (defining relevance to this BMT CTN 1501 trial) if it progresses. Thus, variable time from GVHD onset to requirement of systemic therapy would risk exclusion of otherwise eligible patients if a rigid timeframe was imposed by this trial. Ultimately, we feel that the real starting point of interest is the time at which the treating clinician determines that systemic therapy is needed for GVHD.

A post-randomization time restriction is mandated, allowing a maximum of 24 hours from randomization to first dose of study medication. This will minimize the risk of early GVHD progression due to delayed start of randomized therapy.

13. What is the reasoning for requiring all study assessments from patients with the biomarker status of Ann Arbor 3 or missing?

Patients with the biomarker status of Ann Arbor 3 or missing will have already been started on their randomized therapy, and do have the option to continue on that randomized therapy onward. We feel that the protocol required assessments both highly mirror that of standard clinical assessment schedules after transplant, and also will be instructive from the research standpoint for several reasons. This trial will give us the first insight into how a combined clinical and biomarker-based risk stratified group of GVHD affected subjects respond to an investigational therapy (sirolimus as a steroid-free primary acute GVHD therapy) vs. the

standard of care (prednisone). It is not known or assumed that patients with AA3 status will fail sirolimus, and thus study of their treatment characteristics, requirement for second-line therapy, response and survival outcome is of significant interest.