

## **PROTOCOL SYNOPSIS – BMT CTN PROTOCOL 1501**

### **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**

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**Study Design:** The study is a Phase II randomized, open label, multicenter trial designed to identify whether sirolimus is a potential alternative to prednisone as an up-front treatment for patients with standard-risk acute GVHD defined according to clinical and biomarker-based risk stratification.

Patients with previously untreated, standard-risk acute GVHD, according to the refined Minnesota Criteria, who are in need of systemic therapy, will have a 5 mL blood sample collected prior to randomization to assess their biomarker Ann Arbor Risk status. Ann Arbor scoring results will be provided 48-72 hours after randomization. Patients will begin their study treatment assignments within 24 hours of randomization. Those with biomarker results of combined AA1/2 risk will continue on their randomized study treatment and will be included for primary endpoint analysis and all planned study procedures and assessments. In contrast, patients with AA3 biomarker risk and those patients with missing biomarker results may continue on their randomized therapies or start another therapy at their physicians' discretions. In addition, AA3 risk patients and those with missing results will not be considered in primary endpoint analysis, but will be included in a subset analysis.

**Primary Objective:** The primary objective is to assess the rate of complete remission (CR)/partial remission (PR) on day 28 post-randomization in patients with standard-risk acute GVHD defined by both clinical and AA1/2 risk status.

**Secondary Objectives:** Secondary objectives are to assess the following:

1. The proportion of patients with an acute GVHD response on Day 28 (CR or PR) and who are on a prednisone (or prednisone dose-equivalent corticosteroid) dose of 0.25mg/kg/day or less.
2. Proportions of CR, PR, mixed response, no response and progression among surviving patients at Day 14, 28 and 56.
3. Treatment failure (treatment failure defined as: no response, progression, administration of additional therapy for GVHD

beyond primary therapy, or mortality) at Day 14, 28, and 56. Incidence of chronic GVHD by 6 and 12 months post-randomization.

4. Incidence of systemic infections within 6 months of randomization.
5. Freedom from acute GVHD progression, chronic GVHD, malignancy relapse and mortality at 6 months and 12 months post-randomization.
6. Disease-free and overall survival at 6 and 12 months post randomization.
7. GVHD-free survival at 6 and 12 months post-randomization.
8. Non-relapse mortality at 6 and 12 months post-randomization.

**Exploratory Objectives:**

Exploratory objectives are to assess the following:

1. Steroid-dose (measured in prednisone-equivalent) on Days 7, 14, 21, 28, 35, 42 and 56.
2. Use of topical (skin, GI) agents for acute GVHD therapy.
3. Incidence of discontinuation of immune suppression, and immune suppression discontinuation without GVHD or disease progression/recurrence by Days 56, 180, and 365 post-therapy.
4. Incidence of EBV-associated lymphoproliferative disorder or EBV reactivation requiring therapy
5. Incidence of corticosteroid- and sirolimus-associated complications (collected in all patients):
  - a. Incidence of hyperglycemia (defined as a random glucose >200mg/dL or fasting glucose >126mg/dL) and use of diabetes therapy (use of insulin and/or oral medications to control and/or maintain glucose levels) at baseline, Day 28 and Day 56.
  - b. Change from baseline in functional myopathy score at Day 56 and 6-months post-randomization.
    - i. Hip Flexor and Quadriceps Strength via handheld dynamometer
    - ii. Two Minute Walk Test
    - iii. 5-time Sit-to-Stand
    - iv. Adult Myopathy Assessment Tool (AMAT)
  - c. Incidence of hyperlipidemia as measured by fasting lipid panel at baseline, Days 28, 56 and 180 post-randomization.
  - d. Incidence of post-transplant thrombotic microangiopathy (TMA) by 6 months post-randomization.
6. Proportion of patients requiring therapy for CMV-reactivation by day 56 post-randomization.

7. Change in patient-reported outcomes from enrollment to Day 56, 6 months and 12 months.
  - a. MD Anderson Symptom Inventory (MDASI)
  - b. FACT-BMT
  - c. MOS Short Form 36 (SF-36)
  - d. PedsQL (Pediatric patients)
8. A secondary descriptive analysis will evaluate outcomes for AA3 patients.

**Eligibility:**

Patients of all ages with newly diagnosed standard-risk acute GVHD, diagnosed according to Refined Minnesota Criteria. All allogeneic donor sources and all conditioning regimens are allowed. Biopsy confirmation of GVHD is not required unless institutional practice mandates biopsy confirmation to make a GVHD treatment decision. Patients must have an absolute neutrophil count (ANC) greater than 500/ $\mu$ L. Patients must be able to tolerate oral or enterically-administered medication. Patients must have 5 mL blood samples collected for Ann Arbor Scoring. No previous systemic immune suppressive therapy for acute GVHD is allowed except topical corticosteroid use. Patients receiving sirolimus within 14 days of screening will be excluded. Patients with an active or recent (within 7 days) episode of transplant associated microangiopathy are not eligible. Patients with acute GVHD after donor lymphocyte infusion are not eligible. Patients with clinical presentation resembling de novo chronic GVHD or overlap syndrome are not eligible.

**Treatment Description:**

Patients will be randomly assigned 1:1 to sirolimus vs. prednisone at 2mg/kg/day starting dose. Sirolimus will be loaded and then kept at maintenance dosing for target therapeutic levels for minimum duration through Day 56 post-randomization. Prednisone will be kept at 2mg/kg/day x 3 days, and then tapered according to individual treating clinician judgment.

**Accrual Objective:**

150 total patients will be enrolled and randomized 1:1 to sirolimus vs. prednisone. It is anticipated that ~20% of randomized patients will have AA3 status or missing biomarker results resulting in 120 patients for the analysis of the primary endpoint.

**Accrual Period:**

The estimated accrual period is 2 years.

**Study Duration:**

Patients will be followed for 12 months following initiation of therapy.

**Safety Monitoring:**

The rate of failure of sirolimus therapy by Day 42 post-randomization, defined as the addition of a systemic immune suppressive therapy beyond prednisone among those patients originally treated with sirolimus, will be monitored using a sequential probability ratio test (SPRT) for binary data. The SPRT will contrast a 25% and 50% 42-day rate of sirolimus failure. Day 56 mortality will also be assessed for safety monitoring using a censored exponential SPRT contrasting a 10% and 25% rate of overall mortality.