BMT CTN PROTOCOL #0801

A Phase II/III Randomized, Multicenter Trial Comparing Sirolimus plus Prednisone, Sirolimus/Extracorporeal Photopheresis plus Prednisone, and Sirolimus/Calcineurin Inhibitor plus Prednisone for the Treatment of Chronic Graft-versus-Host Disease

Summary of Modifications from Version 5.0 to Version 6.0

§*2.3.1 Patient Inclusion Criteria and Synopsis Eligibility - Inclusions*: Previously untreated (newly diagnosed) as defined by having received < 14 days of prednisone (or equivalent) before enrollment/randomization to study therapy.

§*2.3.2 #7 Patient Exclusion Criteria and Synopsis Eligibility - Exclusions:*

- Creatinine clearance < 50 mL/min/1.73 m2 or a serum creatinine based on the Cockcroft-Gault formula (adults) or Schwartz formula (age ~~<~~ less than or equal to 12 years)
- Adults: Creatinine clearance (mL/min/1.73m^2) = eC_{Cr} x 1.73 / BSA (m^2)

§*2.5.2.3 Targeting CNI levels:* Whole blood levels of CNIs will be measured by high performance liquid chromatography (HPLC) or HPLC with tandem mass spectrometric detection (preferred methods) or equivalent method with correlation coefficient ≥ 0.90.

§4.3 Treatment Scheduling: Treatment scheduling begins as soon as possible after a patient has undergone baseline screening evaluations and randomization in AdvantageEDC (see Section 4.4, and in particular, baseline screening Section 4.4.1.1).

Table 4.4a Study Assessment Schedule: Added "X" to month 1 for Serum Cholesterol/Triglycerides[5] and footnote 5, Cholesterol at one month

§4.4.1.1 Pre-study evaluations: The following observations should be made at enrollment/randomization +/- 14 days ~~within 14 days before initiation of study therapy~~

§4.4.1.1 Pre-study evaluations , §4.4.1.2 Study Evaluation, Table 4.4.a Study Assessment Schedule: The Comprehensive Chronic GVHD assessment includes the provider survey, the patient survey, and three functional tests (2 minute walk, grip test and Schirmer's eye exam) at baseline, months 2, 6, 12, 24, and 36. The three functional tests (2 minute walk, the grip test and Schirmer's eye exam) are optional at each of these visits.

§5.1.1 Accrual: It is estimated that ~~5~~ 7 years of accrual (3 years for phase II study) will be necessary to enroll the targeted sample size. Both Core and Affiliate Centers will enroll patients on this study. Accrual will be reported by race, ethnicity, gender, age (children defined as < 17 years). Accrual will not be halted while waiting for the 6-month response assessment on the last patient enrolled in the Phase II study; over-run of the Phase II accrual target is considered acceptable as long as there are no safety concerns.

§5.1.4 Primary Hypotheses: H0~~a~~:p_{SP}= p_{SPC} against the alternatives H1~~a~~: p_{SP} >p_{SPC}

§5.2 Details of Study Design and Interim Monitoring Plan for Efficacy and Futility:

- The primary objective of the Phase II …The SP treatment will not be considered further if the Z statistic comparing its CR/PR rate to the SPC arm is ≤ 0.9. This is approximately equivalent to rejecting the SP treatment for further consideration if its CR/PR rate is not at least ~~10%~~ 9% better than the SPC arm, assuming an approximately 40% baseline CR+PR rate….
- *Table 5.2 Boundary Values for Interim Monitoring*

Interim Analysis	# Patients evaluable per treatment arm	Boundary	Decision
1	50 evaluable at 6 months	$Z_6 \leq 0.9$	~~No treatments~~ SP not sufficiently promising in terms of 6-month CR+PR rate; stop study

§5.3 Operating Characteristics and Power Considerations: …This study design has at least 80% power to identify a 20% improvement in both 6-month CR+PR rates and 24-month CR rates between the SP arm and the SPC arm ~~when the SPE arm is 20% better than the SPC arm on both outcomes and 20% better than the SP arm on 6-month CR+PR rate. While these configurations illustrate the power when the SPE arm is the best, the power would be the same if instead the SP arm was the best.~~ Also worth noting, if the SP~~E~~ arm is 20% better than the SPC arm ~~other arms~~ on the 6-month CR+PR rate, there is only a ~~10%~~ 13% chance of stopping the study for futility at the first Phase II analysis.

§5.4.1 Mortality:

- The actual operating characteristics of the truncated test, shown in Table 5.4.a, were determined in a simulation study that assumed uniform accrual of 150 individuals over a ~~five~~ seven-year time period, and exponential time to failure after randomization.
- *Table 5.4.a Operating Characteristics of Sequential Testing Procedure From a Simulation Study with 10,000 Replications, Day 56 Mortality*:

True 56-Day Rate	20%	30%	35%	40%
Probability Reject Null after 50 pts	0.034	0.379	0.660	~~0.855~~ 0.868
Probability Reject Null after 150 pts	0.052	0.756	0.971	0.999
Mean Month Stopped	~~59.7~~ 82.7	~~33.3~~ 45.5	~~19.1~~ 26.4	~~12.7~~ 17.0
Mean # Endpoints in 56 Days	28.9	~~24.2~~ 23.9	~~16.1~~ 16.0	~~12.0~~ 11.7
Mean # Patients Enrolled	144.6	~~82.3~~ 80.7	~~47.9~~ 47.4	~~32.0~~ 30.6

- For example…When the true 56-day mortality rate is 30%, on average, the DSMB will be consulted ~~33~~ 45 months after opening, when 24 events have been observed in ~~82~~ 81 patients. For a treatment arm which only enrolls up to 50 patients, the stopping rule will have ~~85%~~ 87% power to reject the null hypothesis when the Day 56 mortality rate is 40%.

§5.4.2 Non-hematologic Toxicities:

- The actual operating characteristics of this truncated test, shown in Table 5.4.b, were determined in a simulation study that assumed uniform accrual of 150 individuals over a ~~five~~ seven-year time period
- *Table 5.4.b Operating Characteristics of Sequential Testing Procedure From a Simulation Study with 10,000 Replications, Day 56 Incidence of TMA*

True 56-Day Rate	20%	30%	35%	40%
Probability Reject Null after 50 pts	0.038	0.226	0.546	0.818
Probability Reject Null after 150 pts	0.049	0.379	0.856	0.991
Mean Month Stopped	~~59.7~~ 82.8	~~46.9~~ 64.6	~~26.6~~ 36.3	~~14.6~~ 19.9
Mean # Endpoints in 56 Days	14.4	16.8	12.4	~~8.1~~ 8.2
Mean # Patients Enrolled	144.3	~~112.6~~ 112.0	~~62.2~~ 61.8	~~32.4~~ 32.8

- For example… When the true 56-day TMA rate is 20%, on average, the DSMB will be consulted ~~27~~ 36 months after opening, when 12 events have been observed in 62 patients. For a treatment arm which only enrolls up to 50 patients, the stopping guidelines will have 82% power to reject the null hypothesis when the ~~d~~Day 56 TMA rate is 25%.

Appendix B, Patient Consent

- *Introduction (page B-3)*: ~~Because you~~ In this study, chronic GVHD ~~that is considered hisgh risk or resistant, you will also take~~ will be treated with another drug (sirolimus) in addition to either a corticosteroid or a corticosteroid and a calcineurin inhibitor…
- *1. Background (page B-4)*: Sirolimus, cyclosporine and tacrolimus ~~both~~ all work by blocking the growth of new immune cells that can cause chronic GVHD
- *4.Procedures - Before You Start Your Treatment (page B-6)*:
  - Comprehensive Chronic GVHD assessment [to include provider survey, patient survey, 2 minute walk (optional), grip test (optional) and Schirmer's eye exam optional)]
  - ~~Heart and l~~Lung function
- *Study Participation (page B-7):*

2-Drug Treatment
▪ Prednisone: once each day until 2 weeks of improvement in GVHD symptoms is ~~are~~ observed and then slowly lowered and then stopped ▪ Sirolimus: once each day until all prednisone has stopped. After up to 3 months of stable improvement is observed, the amount of sirolimus will be slowly lowered and then stopped

3-Drug Treatment
▪ Prednisone: once each day until 2 weeks of improvement in GVHD symptoms is ~~are~~ observed and then slowly lowered and then stopped. ▪ Sirolimus: once each day. ▪ CNI: two times each day.

- *Study Evaluations (page B-7):*
  - History, physical exam, ~~height~~ and weight at 2, 3, 6, 12, 24 and 36 months
  - Comprehensive Chronic GVHD assessment [to include provider survey, patient survey, 2 minute walk (optional), grip test (optional) and Schirmer's eye exam (optional)] to measure your response to treatment at 2, 6, 12, 24 and 36 months
  - Routine blood tests, including: cell counts, ~~cholesterol~~ and liver and kidney function, at least weekly for the first 4 weeks
  - Cholesterol tests at 1, 2, 3, 6, and 12 months
- *16. Web Information*: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include

information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time