BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN PROTOCOL #1202

Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic HCT

The significant change in the protocol is the enrollment of 200 African American and 200 pediatric participants upon reaching the initial accrual goal of 1500 patients. Deletions to the protocol are indicated in strike-out text. Additions are noted in underlined text.

Changes to the Protocol

- *§Cover page – list of participating centers updated*

- *§Protocol Synopsis – Accrual Objective:* A minimum ~~maximum~~ of 1,500 patients will be enrolled.

- *§Table of Contents:*
  5.4. African American Cohort.....**Error! Bookmark not defined.**
  5.5. Pediatric Cohort .....**Error! Bookmark not defined.**

- *§Eligibility – 2.1 – Inclusion Criteria Hematopoietic Stem Cell Recipients*
  2. Patients with any malignant or non-malignant hematologic disorder will be eligible for enrollment on this protocol. Upon reaching accrual of 1500 patients, only non-Caucasian adults and pediatric participants will be eligible for enrollment. A subset of 240 sequential patients with acute leukemia in first or second remission will also provide research samples for gene expression studies. A minimum of 200 African American participants will be enrolled on this protocol.
  3. Children may participate in this study but must weigh at least 10 kilograms given the volume (100 mL) and number of blood draws during this study (see Section 4.3.3 for blood volume adjustments for patients weighing between 10 and 20 kg). Subjects must weigh at least 30 kg to provide research samples for gene expression studies (additional 40 mL). A minimum of 200 pediatric participants, defined as <18 years at the time of enrollment, will be enrolled on this protocol.

- *§Chapter 4.1 – Enrollment Procedures:* Prior to initiation of conditioning regimen, anauthorized user at the transplant center enters the patient demographics, consent date, and proposed start date for conditioning ~~and proposed transplant date~~ into Segment A in AdvantageEDC.

- *§Chapter 4.2.1:* A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data and Coordinating Center's (DCC)

master database or until an exception is granted and entered into the Missing Form Exception File, as detailed in the BMT CTN AdvantageEDC℠ User's Guide.~~Biomarker Data Management Handbook.~~

- *§Table 4.2.1 - Follow-Up Schedule:* ± ~~4~~ 3 Days to Day 100 Post-HCT

- *§Table 4.3 – BMT CTN 1202 Recipient Sample Collection Schedule:*
  - All ~~1500~~ Patients.
  - This is a subset of the enrolled~~1500~~ patients and will require additional samples to be collected at Days 21, 56 and 90 for gene expression studies.

- *§Table .5.4:* Table 5.~~4~~3.1

- *§5.4: African American Cohort (NEW)*
  Table 5.4 shows the minimum detectable difference in gene frequency among African American recipients compared to Caucasian recipients with at least 80% power for a sample size of 200 African Americans and 1200 Caucasians. The detectable difference was calculated for various gene frequencies among Caucasians and for various numbers of genes being tested simultaneously using a two-sided overall type I error rate of 0.05. Bonferroni correction was used to correct for multiple comparisons in scenarios where two or more genes are being tested simultaneously. When only one gene is considered, the proposed sample size provides sufficient power to detect a minimum difference of 8% - 11% in gene frequency in African American recipients compared to Caucasian recipients. When the frequencies of 50 genes are compared simultaneously, this study is powered to detect a minimum change of 13% - 16%.

Table 5.4 Detectable difference in gene frequency among African American recipients compared to Caucasian recipients with 80% power

Number of genes	Gene frequency in Caucasian population				
	10%	20%	30%	40%	50%
1	08%	10%	11%	11%	11%
5	10%	12%	13%	13%	13%
10	11%	13%	14%	14%	14%
50	13%	15%	16%	16%	16%

§5.5 Pediatric Cohort (NEW)

One of the hypotheses to address is whether the concentration of GVHD biomarkers is lower in children than in adults at the time of GVHD onset. The power to detect a two-fold difference in biomarker concentration with a coefficient of variation (CV) of 2 was calculated for various rates of grade II- IV GVHD (Table 2) using a two-sided overall type I error of 0.05. Bonferroni correction was used to correct for multiple comparisons in scenarios where two or more biomarkers are being compared simultaneously. Assuming Grade II – IV GVHD occurs in 45% of children and 50% of adults, there is more than 90%

power to detect a two-fold difference in biomarker concentration between children compared to adults when up to 50 biomarkers are compared simultaneously. When Grade II – IV GVHD occurs in 35% of children and 40% of adults, there is more than 90% power to detect a difference of this size when up to 10 biomarkers are compared simultaneously and there is 83% power when 50 biomarkers are compared simultaneously.

Table 5.5 Power to detect a two-fold difference in biomarker concentration between children and adults with CV=2

Number of biomarkers tested	GVHD probability in Children vs. Adults (n_1 = number of children, n_2 = number of adults)		
	45% vs. 50% (n_1=90, n_2=650)	40% vs. 45% (n_1=80, n_2=585)	35% vs. 40% (n_1=70, n_2=520)
1	.99	.99	.98
5	.98	.97	.95
10	.97	.96	.92
50	.93	.89	.83

Changes to the Consent Form (Appendix B)

- *Page B-3:* This study will include at least ~~about~~1,500 participants enrolled over a 4 year period.
- *Page B-4:* All research samples will be coded ~~given a number that cannot be linked to you~~.

Changes to the Assent Form (Appendix B)

- *Page B-12:* This study will include at least ~~about~~1,500 people.