

# IMPORTANCE OF THE QUESTIONS BEING ADDRESSED

# FAQs for BMT CTN PROTOCOL 1203

**A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls**

1. **Why run a GVHD phase II prophylaxis trial?**

Graft-versus-host disease (GVHD) remains one of the greatest barriers to successful allogeneic transplants. Several participating BMT CTN core centers are working on ways to abrogate this complication without increasing disease relapse. The premise for a randomized phase II clinical trial is to test novel and promising GVHD prophylaxis approaches that could then be tested in a phase III setting. The BMT CTN 1203 clinical trial will test three novel approaches in a multi-center setting and compare each intervention to a large contemporary control cohort. Additionally, none of the regimens that were based on a standard calcineurin inhibitor backbone were sufficiently studied to warrant moving directly to a phase III clinical trial.

1. **How the interventions used in this study were selected?**

The BMT CTN GVHD committee led a benchmark analysis to assess six different single center GVHD prophylaxis approaches comparing with standard tacrolimus/methotrexate prophylaxis using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The benchmark analysis compared each of these 6 interventions directly with a control group adjusting for differences in the populations related to patient age, diseases, disease status, conditioning intensity, donor type and HLA matching. The interventions selected for this trial were associated with better acute or chronic GVHD outcomes compared to the control group. All three interventions were tested after reduced intensity conditioning and the results appeared promising for further study in a multicenter setting[1-3](#_ENREF_1).

1. **Why select a composite primary endpoint?**

Historically, trials that tested new GVHD prophylaxis strategies evaluated primarily the rate of acute GVHD and most recently, acute GVHD-free survival (BMT CTN 0402). As these approaches are potentially more immunosuppressive than standard GVHD prophylaxis regimens, an increase in malignant disease relapse is a potential risk. In parallel to the assessment of promising GVHD prophylaxis approaches described above the BMT CTN GVHD committee discussed novel end points to determine success that not only included GVHD and survival but accounted disease relapse and combined GVHD forms that would have a significant impact in the health of patients. Among the endpoints discussed, the requirement of prolonged chronic immunosuppression was of interested as it represented ongoing problems with chronic GVHD and a higher risk for later mortality. Due to absence of baseline data and the multitude of practice patterns related to tapering of immunosuppression this end point at the current time was not optimal. It was however included as a secondary endpoint and expressed as immunosuppression and relapse-free survival. The composite endpoint that could be easily applied in a clinical was a time to event assessment of GVHD/relapse-free survival (GRFS). This endpoint defines the events as grade 3-4 acute GVHD, chronic GVHD requiring systemic therapy, relapse and death. The rationale of assessing to forms of GVHD was that different approaches would have a differential effect in acute and chronic GVHD. Additionally, among all forms of acute GVHD, grades 3 and 4 were significantly associated with mortality. According to the benchmark analysis, 85% of patients who developed grade 3 to 4 acute GVHD would have developed chronic GVHD, relapsed or died later during the first year of transplant.

On applying this composite endpoint to the control group in the benchmark analysis, the baseline rate was 23% for recipients of reduced intensity conditioning regimens and 21% for recipients of myeloablative regimens. Thus, the current transplant practice, only a fifth of the patients alive by the end of the first year from transplant are free from GVHD and relapse complications. Improvement of this outcome would advance the field of transplantation.

1. **Why not randomize the control arm?**

We considered a randomized control arm. However, since this is not a phase III trial, the benefit of randomization was offset by the significant increase in study size, accrual barriers (consenting to a 4 arm randomized trial was felt to be more onerous), and cost. Further, using a contemporaneous control arm allowed for its efficient accrual from BMT CTN centers not participating in the BMT CTN 1203, at a sample size (270 controls) sufficient to allow statistical adjustment for heterogeneity of patient and disease factors in the 3 treatment arms (90 patients each).

1. **How will the CIBMTR database be used to select the controls?**

The study will prospectively accrue contemporaneous controls from US transplant centers not accruing to BMT CTN1203 study. The approach of establishing the control will be similar to a prospective cohort analysis with the following steps: invite transplant centers to participate, centers would need to comply with on time data reporting, active monitoring of data reporting, supplemental data to refine information related to GVHD manifestation and use of immunosuppressive drugs, outcome adjudication review, matching and analyses. The control group from participating CIBMTR centers will be identified after fulfilling the same eligibility as the patients enrolled in the intervention arms. The plan is to enroll a minimum of three times the amount of controls as of patients in each intervention arm. Since the benchmark analysis for this primary endpoint described above demonstrated that disease is a significant covariate associated with the GRFS endpoint, patients from the intervention arm will be matched according to disease. At the half way point in the accrual to the intervention arms demographic characteristics will be compared with the control. Depending on this comparison, additional controls might be needed to minimize heterogeneity.

1. **Why restrict the study population to recipients of mobilized peripheral blood stem cell (PBSC) grafts?**

PBSC grafts comprise the vast majority of RIC transplantations in the US today[4](#_ENREF_4). There is randomized data in myeloablative transplantation indicating lower GVHD rates and similar survival with bone marrow (BM) versus PBSC grafts[5](#_ENREF_5). However, RIC transplantation (critically dependent on immunologic graft-versus-leukemia effect), does not have such data, and may indeed benefit from the higher dose of donor T cells included with mobilized PBSC grafts. In order to reduce heterogeneity of graft sources impacting our study endpoint, we have restricted the study to PBSC grafts, since additional randomization or stratification for PBSC vs. BM graft variable was not feasible in a phase II study context.

1. **Why exclude children?**

The interventions chosen for this trial were primarily tested in the adult population. Of the three intervention arms, only post-transplant cyclophosphamide was formally tested in the pediatric population[3](#_ENREF_3). Maraviroc is currently FDA-approved for adults only and the appropriate dose in children is unknown. Studies that define the dose and toxicities of maraviroc in children are under way and preliminary results are not expected before 2015. Bortezomib has been tested in the pediatric population in several clinical scenarios but not in the setting of stem cell transplantation and its risks and benefits in this situation are unknown. In addition, the use of RIC regimens in children for the indications listed in this protocol is fairly uncommon and it was therefore decided to limit this study to adult accrual.

1. **How is the heterogeneity of different diseases being addressed in this trial?**

The trial was designed to include a wide range of hematologic malignancies that are currently the most common indications for allogeneic RIC transplants. A central goal was to assure rapid accrual and applicability of the results to a broad patient population, allowing rapid translation to a phase III trial and to a new standard of care. The choice of contemporaneous controls based on similar eligibility criteria (including disease categories) and not historical controls from the CIBMTR registry ensures a relevant comparator group for the 3 interventions. According to the benchmark analysis described above, the GRFS primary endpoint identified 2 disease groups that had different outcomes - low risk (AML, ALL, CML, NHL) and high risk (CLL, MDS). The GFRS rates within the first year of transplantation for these disease groups were 24-30% and 12-16% respectively. In order to minimize the differential impact of disease, the protocol will stratify patients into low-risk and high-risk disease strata, according to the GRFS endpoint. The CIBMTR controls will be matched according to the same disease categories.

1. **How were the reduced intensity/nonmyeloablative regimens selected?**

The specific regimens were selected based on a review of the most common conditioning regimens that were reported to CIBMTR in 2011 and met CIBMTR criteria for reduced intensity (n=1913). These regimens have been previously studied and their outcomes have been reported in the literature[3](#_ENREF_3),[6-9](#_ENREF_6). They have garnered widespread acceptance in the transplant community such that they are considered “standard of care”. The use of ATG and alemtuzumab were excluded following a recent CIBMTR analysis, which suggested adverse survival outcomes with the addition of ATG or alemtuzumab to RIC regimens[10](#_ENREF_10).

1. **Is this trial feasible?**

Each year, approximately 1,800 patients undergo stem cell transplantation with reduced intensity conditioning for the diseases listed in this protocol according to CIBMTR data. The feasibility of each of the treatment arms has been demonstrated in phase I/II and phase II studies and each of the interventions has shown sufficient promise to be included in this randomized phase II multi-center study. Competing trials with overlapping eligibility criteria may affect enrollment in major transplant centers but the liberal eligibility criteria and the growing number of RIC transplants will likely enhance overall enrollment. The data collection for the control arm is based on routine reporting to the CIBMTR registry with only minimal supplemental data required. Therefore, it is believed that contemporaneous control data will be available for the analysis of the trial’s end-points.

1. **What is the impact of multiple comparisons on the type 1 error?**

There are 3 treatment arms each being compared to the control arm at the 5% one-sided significance level. The overall type I error rate, or the likelihood that at least one of the treatments is incorrectly identified as promising, is approximately 11-13% (one-sided) based on simulations. Although this rate may seem somewhat high, in phase 2 cancer trials, higher type I error rates of 10-15% are sometimes used in order to ensure adequate power for a feasible sample size. Stricter control of the type I error rate is reserved for a follow-on phase 3 trial.

1. **Why are the randomized treatment interventions not being formally compared statistically?**

The main objective of the trial is to identify which, if any, of these interventions is sufficiently promising relative to a tacrolimus+methotrexate control group to warrant further study in a phase III trial. This study is not adequately powered to detect reasonable differences among the randomized treatment arms, especially given the increased number of multiple comparisons one must account for.

1. **Accrual Estimates: *please see separate document***

**References**

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