FAQs for BMT CTN PROTOCOL 1703 & Mi-Immune

A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

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Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation (Mi-Immune)

1. Why run a GVHD phase III prophylaxis trial?

Graft-versus-Host-Disease (GVHD) is an important cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT) and remains one of the greatest barriers to successful allogeneic transplants. BMT CTN 1703 is a multicenter Phase III clinical trial, that will evaluate 2 GVHD prophylaxis approaches for their efficacies in improving the proportion of patients who do not develop severe acute GVHD, chronic GVHD that requires systemic therapy, disease progression, or relapse by one-year post-transplant. This pivotal trial has the potential to change clinical practice if it demonstrates the superiority of post-transplant cyclophosphamide/tacrolimus/mycophenolate mofetil (PT-CY/Tac/MMF) in patients undergoing reduced-intensity conditioning (RIC) allogeneic HCT.

2. How was the investigational arm used in this study selected?

The PT-CY/Tac/MMF constitutes the investigation arm of BMT CTN 1703. The recently concluded BMT CTN 1203 was foundational to the design of the current 1703 protocol. BMT CTN 1203 compared PT-CY/Tac/MMF (n=92), Tac/methotrexate/bortezomib (n=89) and Tac/methotrexate/maraviroc (n=92) to 224 CIBMTR controls who received Tac/methotrexate-based GVHD prophylaxis, with the intent of testing the best approach in a future randomized phase III trial. In the BMT CTN 1203, PT-CY/Tac/MMF was the only study arm that showed an improved GVHD-free relapse-free survival (GRFS) relative to controls[1], and was thus selected as the investigational arm of the confirmatory, phase III trial (BMT CTN 1703). In addition to 1203 data, the possibility of testing other novel GVHD prophylactic approaches as additional arms on BMT CTN 1703 was carefully considered by the BMT CTN Steering Committee. The Network Core and Affiliate Centers were invited to propose additional potential GVHD prophylactic approaches that could be considered for inclusion in the current trial. Several candidate regimens were considered (HDAC inhibitor-based regimen, PT-CY in combination with proteasome inhibitor, sirolimus-based regimens and tac/MMF combination). Careful evaluation of these regimens either demonstrated no significant GRFS difference when compared to CIBMTR Tac/methotrexate controls (used in BMT CTN 1203) or some prophylactic approaches had only been investigated in the context only 2GY TBI-based non-myeloablative conditioning regimens (limited the generalizability of efficacy data). All of the above carefully reviewed and discussed caveats supported the selection of PT-CY/Tac/MMF as the sole investigational arm of BMT CTN 1703.
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3. Why select a composite primary endpoint?

Historically, trials that tested new GVHD prophylaxis strategies evaluated primarily the rate of acute GVHD or acute GVHD-free survival. Unfortunately, while a novel GVHD prophylactic approach could be effective in preventing the development of GVHD, owing to profound immunosuppression it can also be associated with higher relapse and/or non-relapse mortality risk (e.g. due to infectious complications). In parallel to the assessment of promising GVHD prophylaxis approaches described above the BMT CTN GVHD committee previously discussed novel end points to determine success that not only included GVHD but also accounted for disease relapse and survival. The composite endpoint GRFS was selected and previously tested as the primary endpoint in BMT CTN 1203 protocol. On applying this composite endpoint to CIBMTR patients in the benchmark analysis, the baseline rate was only 23% for recipients of RIC regimens. Thus, with 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.

4. 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[2]. There are randomized data in myeloablative transplantation indicating lower GVHD rates and similar survival with bone marrow versus PBSC grafts[3]. However, RIC transplantation (critically dependent on immunologic graft-versus-tumor effects), does not have such data, and may indeed benefit from the higher dose of donor T cells included with mobilized PBSC grafts. To reduce heterogeneity of graft sources impacting our study endpoint, consistent with the prior BMT CTN 1203 study, we have restricted the study to PBSC grafts. Moreover, since only about 5% of RIC in the U.S. use bone marrow as a graft source, exclusion of these cases is unlikely to impact the feasibility of BMT CTN 1703.

5. Why exclude children?

The inclusion of pediatric cases was considered carefully by both the BMT CTN 1703 protocol team and the BMT CTN Steering Committee. The general consensus, after taking into account input from representatives of pediatric transplant centers was not to include pediatric cases because of two main reasons: (1) The use of PBSC as a graft source (an eligibility criterion on BMT CTN 1703) is uncommonly used in pediatric centers and was considered an accrual barrier. (2) The use of RIC regimens in children with good performance status and limited comorbidities for the indications listed in this protocol is uncommon. Hence it was decided to limit this study to adult accrual.

6. 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. However, inclusion of different hematological malignances with varying remission statuses (associated with different relapse and/or mortality risk) can impact the primary endpoint GRFS, if two study arms are imbalanced. In order to minimize the differential impact of disease, randomization will be stratified by disease risk using Disease Risk Index (DRI)[4]. The DRI is a validated tool to categorize groups of patients undergoing allogeneic HCT for hematologic malignancy by disease risk. Stratifying randomization according to DRI will ensure that the two arms of BMT CTN 1703 are balanced in terms of disease relapse and mortality risk.

7. How were the reduced intensity/nonmyeloablative regimens selected?

In the prior BMT CTN 1203 protocol (that is foundational to the design of current BMT CTN 1703 study), the selected specific regimens represented the most common conditioning regimens that were reported to CIBMTR and met the Consensus criteria for reduced intensity (n=1913). All of these regimens have been previously studied and their outcomes have been reported in the literature[5-8]. They have garnered widespread acceptance in the transplant community such that they are considered "standard of care". The use of ATG and alemtuzumab is not permitted, owing to known effects of these agents on GVHD and relapse rates in the RIC setting.

8. Is this trial feasible?

Each year, approximately 2,000 patients (~980 patients in BMT CTN Core Centers and ~1000 in BMT CTN Affiliate Centers) undergo hematopoietic cell transplantation with RIC regimens for the diseases listed in this protocol, according to CIBMTR data. Among the 2,000 potential cases approximately 1,200 every year would be eligible for BMT CTN 1703 in the U.S. (after restricting to eligible histologies, donor type, graft source, patient performance status and after excluding patients receiving in vivo T-cell depletion with antilymphocyte globulin or alemtuzumab). Competing trials with overlapping eligibility criteria may affect enrollment in some transplant centers but the liberal eligibility criteria and the growing number of RIC transplants will likely enhance overall enrollment. BMT CTN 1203 completed accrual 6 months ahead of projection.

9. Are there any plans in place to stop enrollment if one arm of the protocol looks superior compared to the other arm?

Yes, the study will consist of one interim analysis for efficacy after the required total number of events is reached in all evaluable patients for the primary endpoint to be reviewed by the NHLBI-appointed Data and Safety Monitoring Board (DSMB). An interim analysis for efficacy will be conducted when 60% of the data are collected. If the study is stopped for efficacy then all subsequent patients will be enrolled on the superior treatment arm where the study will proceed until the targeted sample size for Mi-Immune is reached.

10. Is there a need for a multi-center network to meet the objectives?

Yes. Although GVHD is a common post-transplant complication, no single center treats sufficient numbers of patients to complete this study in a reasonable timeframe.

11. What are the proposed plans for data acquisition, transfer, management and analysis?

A web-based data entry platform will be used for all BMT CTN supplemental forms. Data are transmitted via an encrypted link between the web server and browser using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Data Management Handbook will be developed for reference.

Missing forms reports are updated daily. Queries will be developed to check for missing and inconsistent data. Queries will be distributed to the centers at least monthly.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the statistical analysis plans outlined in the protocol.

12. Are there any specific study training plans necessary to accomplish the research goals (e.g. workshops, study certification)?

Site coordinators will need to participate in a clinical site initiation call with the protocol coordinator. No other certifications or workshops will be required for this study.

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

14. What is "Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation (Mi-Immune)"?

Mi-Immune represents an ancillary study that will be offered to a subset of the 1703 cohort, where **additional** key precision medicine and systems biology questions will be explored.

15. What are the objectives of this ancillary study?

The objectives are to determine the association between gut microbiome diversity (at baseline and at the time of hematopoietic recovery) and 1-year cumulative incidences of non-relapse mortality, acute and chronic GVHD, and overall survival (OS). Furthermore, the impact of the two GVHD prophylaxis regimens (tac/mtx vs. PT-CY/tac/mmf) on microbiome diversity and T-cell receptor diversity at specified time points will be determined. Additionally, the impact of volume of antimicrobial exposure on cumulative incidence of acute and chronic GVHD, as well as OS will be determined. Finally, the impact of urine metabolites at the time of hematopoietic recovery on cumulative incidence of acute GVHD will be determined.

16. What are the eligibility criteria?

Mi-Immune will only enroll patients who are enrolled on 1703, and therefore, the same inclusion/exclusion criteria defined in 1703 will be followed.

17. How will patients enrolled onto 1703 be co-enrolled to Mi-Immune?

The informed consent form for 1703 will allow the patient to opt-in or opt-out to Mi-Immune. Once the target sample size for Mi-Immune has been reached, additional patients will only be enrolled to 1703 and Mi-Immune will be closed for accrual.

18. How many patients from 1703 will be co-enrolled to Mi-Immune?

Seventy percent of the subjects enrolled to 1703 will be co-enrolled to Mi-Immune for a total sample size of 300. The targeted sample size of 300 evaluable patients would have at least 85% power to detect a 20% difference in 1-year non-relapse mortality between any two microbiome diversity groups.

19. What is the estimated accrual time?

3 years

20. Will patients enrolled onto Mi-Immune have a different follow-up schedule compared to 1703 patients not enrolled onto Mi-Immune?

The follow-up schedule is the same for both studies. If the patient elected to opt-in to Mi-Immune, there will be one additional sample collection at 24 months.

21. What samples/clinical data will be collected from subjects enrolled to Mi-Immune?

Please refer to Table 4.2.5 in Appendix J for details. Essentially, peripheral blood, stool and urine samples will be collected from subjects and their related donors. For related and unrelated donors, the product WBC will be collected from the product bag for WBC cell recovery and cryopreservation. Additionally, Mi-Immune will collect detailed infection data and antimicrobial use as this data is critical to understanding alterations in the microbiome. Infections, a frequent and serious complication of transplant, require certain detailed information to understand the impact on transplant outcomes and the microbiome. We will collect data on specific infection forms every 2 weeks through day 100 (per Table 4.2.5). Thereafter, a short form is used for current infection-related data at the time the form is due.

22. Why are related donors being asked to participate in the Mi-Immune research studies?

Having the opportunity to also analyze research samples from related donors will add value to understanding the potential donor-related factors that might influence patient transplant outcomes. We are therefore providing, in the context of 1703, an opportunity for related donors to provide pre-collection research samples for Mi-Immune and future BMT-related research.

23. Are there any specific study training plans necessary to accomplish the research goals of Mi-Immune?

Detailed instructions for the collection, temporary storage and transport to clinical sites, and final FedEx shipping to the BMT CTN Biorepository for all inpatient and outpatient urine, stool and peripheral blood research samples will be provided in the 1703 Research Sample Information Guide and briefly reviewed in clinical site initiation calls.

24. What are the recruitment strategies if applicable, and proposed plans for monitoring study accrual?

The protocol team for 1703/Mi-Immune will closely monitor the co-enrollment rate and will define thresholds that would signal Mi-Immune might fall short of enrolling 70% of the parent protocol. The protocol team will meet frequently to discuss enrollment and ways to improve enrollment. Action plans will be put into place to address any shortfalls.

25. Since the sample at the time of engraftment will be sufficient to address the primary hypothesis, why are additional samples beyond time of engraftment being collected?

An important ***future*** objective of Mi-Immune is to be positioned to explore a number of questions related to transplant outcomes and complications. However, they are ***not*** currently stated objectives to be addressed in the current study.

26. Why are the samples collected on a weekly basis?

Collecting samples on a weekly basis, even though it requires times and effort commitment, allows for measurement of the biomarker before the event of interest takes place. The alternative approach – event-driven samples – limits our ability to address whether the biomarker level perturbation preceded the event of interest, or was the result of the development of the event of interest.

27. Why are urine samples required?

Urine metabolites such as indoxyl sulphate were shown to function as indirect measure of the diversity of the gut microbiome. Specifically low levels (when gut microbiome diversity is restricted) were shown to correlate with increased risk of acute GVHD. The current study will help confirm these findings.

References

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