

BMT CTN 2503 PTCy Optimization

A Randomized, Multicenter, Phase III Trial Comparing High Dose to Reduced-Dose Cyclophosphamide After Myeloablative HLA-Matched Allogeneic Hematopoietic Cell Transplant

FREQUENTLY ASKED QUESTIONS (FAQs) Version 1.0 dated 24 SEP 2026

1. What is the reason to compare high-dose versus reduced-dose cyclophosphamide?

Despite superior GRFS with high-dose PTCy (defined as 50mg/kg on days +3 and +4) compared with historical platforms, lack of a clear overall survival advantage supports that further improvements in the PTCy platform are warranted. Limitations with PTCy include slower neutrophil engraftment, organ toxicity, infections, and relapse (the leading cause of death after all HCT platforms). Reducing the dose of PTCy has the potential to speed engraftment, reduce organ-specific toxicity (i.e. mucositis, cardiotoxicity, cystitis) associated with high-dose PTCy, and improve T cell engraftment to potentially decrease infections and relapse. However, whether this leads to unacceptable increases in GVHD incidence needs to be studied in a randomized fashion to determine the optimal dose of PTCy.

2. Why was 25 mg/kg selected for the reduced-dose cyclophosphamide?

Murine HCT studies suggest that PTCy 25 mg/kg/day on days +3 and +4 is superior to lower or higher doses. As a result of those studies, several single arm clinical trials have shown that reduced-dose PTCy (defined as 25mg/kg on days +3 and +4) may result in reduced toxicity, while maintaining prevention of severe GVHD. While other doses of Cy have been examined in small studies, this analysis is not powered to examine more than two doses of PTCy or to detect small differences in clinical outcomes between two more similar doses (i.e. 40mg/kg).

3. Why is the primary endpoint being analyzed by the win ratio method?

Many of the contemporary GVHD prophylaxis trials have used a composite primary endpoint of GRFS. While GRFS accounts for several important endpoints in allogeneic HCT, there are significant drawbacks, including equal weighting of each event regardless of clinical importance (i.e. death and grade III-IV acute GVHD are weighted equally) and exclusion of additional clinically relevant endpoints such as significant infections, organ toxicity, and engraftment kinetics. A hierarchical composite endpoint approach using a win ratio analysis allows for differential weighting of a variety of endpoints. This allows us to determine a winner based on the most important clinical outcomes and if ties in a component of the hierarchical primary endpoint occur, we then move on to the next most important clinical outcome until a tie is broken.

4. Why was HLA-matched PBSCT design chosen?

While reduced-dose PTCy has been explored in single arm studies of haploidentical and heavily mismatched unrelated donor settings, results from these studies have included either primarily bone marrow grafts (NCI studies) or have used PBSC with relatively early follow-up (OPTIMIZE trial). Thus, data to support reduced-dose PTCy with PBSC grafts from heavily mismatched donors is more limited, and for this reason, this trial will focus on PBSC grafts from well-matched donors. PBSCT was chosen as a graft source since it is by far the most common graft source utilized in the United States and we wanted the trial to be applicable to common practice. In addition, given that

engraftment is a part of the primary endpoint, then graft source must be uniform.

5. Why are the allowed donors limited to 8/8 and 7/8?

Given that increases in GVHD could be an outcome of reduced-dose PTCy, we wanted to investigate the platform in a well-matched donor setting first, before extending it to highly HLA-mismatched HCT. Outcomes for 7/8 vs. 8/8 are similar, and as such these two donor options have been explored together in many prior studies of well-matched HCT platforms, including BMT CTN 1703. Inclusion of 7/8 donor HCT will allow enrollment of a wider population of patients as nearly 80% of patients will have a 7/8 unrelated donor identifiable on the National Marrow Donor Program registry. However, results from OPTIMIZE will be available later in the year. If these results reflect safety and feasibility of Cy de-escalation with more HLA-mismatched donors, the study team will consider expanding the eligible donor pool accordingly. Conversely, if there are any adverse signals, we may consider limiting enrollment to 8/8 HLA-matched donors.

6. What are the allowable myeloablative conditioning regimens and why?

Allowable myeloablative conditioning (MAC) regimens were selected based on a review of CIBMTR data on the most frequently used MAC regimens that are combined with PTCy. Fludarabine/Busulfan, Fludarabine/Busulfan/Thiotepa, Total Body Irradiation alone, and Fludarabine/ Total Body Irradiation will be allowable regimens (please see the main protocol for dosing details). These regimens encompass >90% of MAC regimens utilized with PTCy across the country according to the CIBMTR data. Not all MAC platforms are allowable because conditioning that includes pre-HCT Cy could influence PTCy pharmacokinetics via Cy mediated induction of metabolism. In addition, we wanted to limit the number of included regimens so that conditioning regimens could be adjusted for in the analyses, which would not be feasible if all possible MAC platforms were included.

7. Why is GCSF required?

One of the components of the hierarchical composite endpoint is time to neutrophil engraftment. Because gCSF can influence time to neutrophil engraftment, we want its administration to be uniform across sites to avoid bias in the results.

8. Why is the Tacrolimus taper per protocol rather than following institutional practice?

Given that GVHD is part of the hierarchical composite primary endpoint, GVHD prophylaxis platforms must be uniform across centers and between the arms to avoid bias. While not all inclusive, the two most common practices for tacrolimus cessation are 1) stopping tacrolimus without taper at 90 days post HCT and 2) beginning taper of tacrolimus at day 90 with cessation by day 180. Therefore, to keep the GVHD prophylaxis more homogenous, we are asking institutions to choose one of these two practices a priori.

9. Are all participants being analyzed or only transplanted participants?

Given that the primary endpoint includes transplant-specific complications, only those patients who are transplanted would be able to be analyzed for the primary endpoint. However, secondary survival analyses may be performed in the intent to treat population.

10. What is the reasoning for a double randomized study?

Over three hundred patients have been treated with reduced-dose PTCy with promising results. However, no randomized studies have compared PTCy doses. The most robust trial design is one that is randomized to avoid bias. Therefore, to determine the optimal dose of PTCy we are conducting a randomized study of high-dose vs. reduced-dose PTCy. If reduced-dose PTCy

improves outcomes compared to high-dose PTCy, this randomized trial could support a change to the standard of care for HLA-matched PBSCT. A companion study in a subset of patients will also explore the influence of resistant potato starch (RPS) (an oral prebiotic) on butyrate levels and the microbiome in patients treated with high-dose PTCy and reduced-dose PTCy. To explore the influence of RPS and avoid bias, patients will be randomized to receive or not receive RPS. Given more limited preliminary data on RPS, this exploratory study is not powered to change the standard of care but will provide evidence for future studies.

11. What is the rationale for not using a double-blind study design?

An assessment of feasibility was conducted regarding a double-blind design and found it would increase the costs tremendously, both at the center level, and centrally, and would make the study infeasible. The Steering Committee felt that omitting blinding was very reasonable, and instituted certain measures to attempt to avoid bias, including: 1) centers specifying tacrolimus taper plans a priori regardless of study arm; b) centers specifying maintenance therapy plans a priori regardless of study arm; c) ensuring that the protocol includes guidance on immunosuppression planning regardless of arm.

12. Why are patients < 10 not allowed to participate in the RPS embedded study?

There are no existing feasibility data in patients <10 years old and thus there were concerns related to dosing and tolerability among younger children. It was felt that rather than introducing it in this multi-center trial, it would be better to first study dosing and feasibility in younger children.

13. What is the rationale for excluding patients who receive RPS from the primary analysis population?

It is possible that administration of RPS will influence the development of GVHD or infections, which are components of the primary endpoint. The primary goal of the study is to determine the optimal Cy dose regardless of RPS, therefore only patients who do not receive RPS will be eligible for the primary comparison of high-dose and reduced-dose PTCy to avoid bias. However, secondary analyses of clinical outcomes will also be explored in the subgroup of patients receiving RPS compared to those not receiving RPS on the companion study. This will facilitate identification of any signal that RPS administration (with either high-dose or reduced-dose PTCy) warrants evaluation in a larger clinical trial.

14. Why are pediatric patients included?

Limiting alkylator exposure has the potential to benefit pediatric patients. If reduced-dose PTCy is found to be superior in adults, but pediatric patients are not included in this trial, then this platform will have limited adoption in pediatric practice. This will potentially lead to worse outcomes and more toxicity for pediatric patients. Given that their clinical outcomes can be distinct from adults, we will plan a secondary analysis in the pediatric subgroup. With regard to RPS, MAC leads to alterations in the microbiome in both pediatric and adult patients. RPS has also been studied and found to be safe and feasible in a small cohort of pediatric patients. Just like adults, pediatric patients have the potential to benefit from microbiome modulation with RPS and therefore should be included in this study.

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

Yes. No single center treats enough patients to complete this study in a reasonable timeframe.

16. Accrual Estimates

Please see separate accrual plan document.