

PROTOCOL SYNOPSIS

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

Co-Principal Investigators: Lori Muffy, M.D., M.S. and Shannon McCurdy, M.D.

Study Design: This study is a randomized, Phase III, open label multicenter trial comparing high-dose to reduced-dose post-transplant cyclophosphamide (PTCy) with standard tacrolimus (Tac) and mycophenolate mofetil (MMF) in patients with hematologic malignancies undergoing allogeneic hematopoietic cell transplantation (HCT) with myeloablative conditioning (MAC) using well-matched (human leukocyte antigen [HLA] 8/8 or 7/8) donors. Patients are randomized 1:1 to the investigational arm (PTCy 25 mg/kg/day on Days +3 and +4) or the conventional arm (PTCy 50 mg/kg/day on Days +3 and +4); all patients will receive MAC peripheral blood stem cell (PBSC) HCT and graft-versus-host disease (GVHD) prophylaxis with PTCy, Tac, and MMF. The primary endpoint is a hierarchical composite compared for superiority using the win ratio method.

Centers will have the option of participating in an exploratory embedded study in which participants will be randomized to receive resistant potato starch (RPS), a microbiome modulating agent, in combination with either PTCy50/Tac/MMF or PTCy25/Tac/MMF. Patients included in this embedded study who receive RPS will not be included in the overall primary efficacy endpoint but will be assessed for biological activity of RPS in combination with both standard and reduced-dose PTCy. Exploratory studies will be performed in all patients on the embedded study. Sites that are enrolling in the embedded study will have to complete their site enrollment in the embedded study before opening the main study. Once enrollment is complete on the embedded study, sites will enroll in the main study.

Primary Objective of the Main Study:

Compare the clinical efficacy of PTCy25/Tac/MMF versus PTCy50/Tac/MMF using a hierarchical composite endpoint assessed with a win ratio design. The endpoint ranks outcomes in the following order: time to death, time to relapse, occurrence of grade 3-4 acute graft-versus-host disease (GVHD), occurrence of moderate/severe chronic GVHD, development of grade 3-4 cardiac toxicity, development of BMT CTN grade 2-3 infection, and time to neutrophil engraftment.

Secondary Objectives of the Main Study:

Compare PTCy25/Tac/MMF versus PTCy50/Tac/MMF across key efficacy and safety outcomes, including overall survival, relapse or progression, relapse-free survival, non-relapse mortality, and GVHD-free/relapse-free survival. Additional comparisons include graft failure, acute and chronic GVHD, infections, cardiac adverse events, engraftment kinetics, and other transplant-related toxicities (e.g., mucositis, sinusoidal obstruction syndrome, cystitis, renal failure). Supportive interventions (e.g., CD34-selected stem cell boost, donor lymphocyte infusion) and patient-reported outcomes will also be evaluated.

Objectives of the RPS Embedded study:

The main objective of the RPS embedded study is to determine the biological activity associated with administering the oral prebiotic RPS, an intestinal microbiome modulating agent with PTCy25/Tac/MMF or PTCy50/Tac/MMF.

Eligibility Criteria:

Eligible participants are aged ≥ 1 (no upper age limit) undergoing first allogeneic hematopoietic cell transplantation (HCT) with myeloablative conditioning for specified hematologic malignancies, including acute leukemias ($\leq 5\%$ marrow blasts), myelodysplastic syndromes ($< 10\%$ blasts), or myeloproliferative neoplasms ($< 10\%$ blasts, excluding myelofibrosis). Patients must have a related or unrelated PBSC donor matched at 7/8 or 8/8 HLA loci and meeting donation criteria. Key eligibility requirements include adequate organ function (cardiac, hepatic, renal, and pulmonary), performance status $\geq 60\%$, and agreement to contraception requirements where applicable. Participants or legal guardians must provide informed consent.

Treatment Description: All patients will receive MAC followed by HLA 8/8 or 7/8 related or unrelated PBSC HCT. Main Study Participants will be randomized 1:1 to one of the following arms:

Investigational Arm of reduced-dose PTCy (PTCy25/Tac/MMF): PTCy will be administered at a dose of 25mg/kg on Days +3 and +4, followed by standard dosing of Tac/MMF starting on Day+5.

Conventional Arm of high dose PTCy (PTCy50/Tac/MMF): PTCy will be administered at a dose of 50mg/kg on Days +3 and +4, followed by standard dosing of Tac/MMF starting on Day+5.

RPS Embedded study: Centers participating in the Embedded study will enroll patients who will be randomized to one of the following arms:

PTCy25/Tac/MMF/RPS: RPS will be administered orally at a dose of 1 packet twice daily starting with the first day of conditioning through Day +100. PTCy will be administered at a dose of 25mg/kg on Days +3 and +4, followed by standard dosing of Tac and MMF starting on Day+5.

PTCy50/Tac/MMF/RPS: RPS will be administered orally at a dose of 1 packet twice daily starting with the first day of conditioning through Day+100. PTCy will be administered at a dose of 50mg/kg on Days +3 and +4, followed by standard dosing of Tac and MMF starting on Day+5.

PTCy25/Tac/MMF/NoRPS: PTCy will be administered at a dose of 25mg/kg on Days +3 and +4, followed by standard dosing of Tac and MMF starting on Day+5.

PTCy50/Tac/MMF/NoRPS: PTCy will be administered at a dose of 50mg/kg on Days +3 and +4, followed by standard dosing of Tac and MMF starting on Day+5.

Accrual Objective: The accrual goal is 306 participants in the main study who will be analyzed for the primary endpoint. In the main study, 153 participants will be randomized to the investigational arm and 153 participants will be randomized to the conventional arm. In the RPS embedded study, 25 participants will be randomized to receive RPS with the investigational arm PTCy dosing and 25 participants will be randomized to receive RPS with the conventional arm PTCy dosing. Of note, 50 patients from the embedded study who are not randomized to RPS will be included in the main study (25 receiving high dose PTCy and 25 receiving reduced-dose PTCy). These patients will be used as a comparison for the RPS cohorts but will also be counted toward the main study's primary and secondary endpoints. Thus, a total

of 356 patients will be enrolled. Additional participants may be screened, consented, and registered to reach accrual goals.

Accrual Period:

The estimated accrual period is 30 months

Study Duration:

Participants will be followed for 1 year following HCT. Long-term follow-up will be performed through CIBMTR reporting.

Pausing Guidelines:

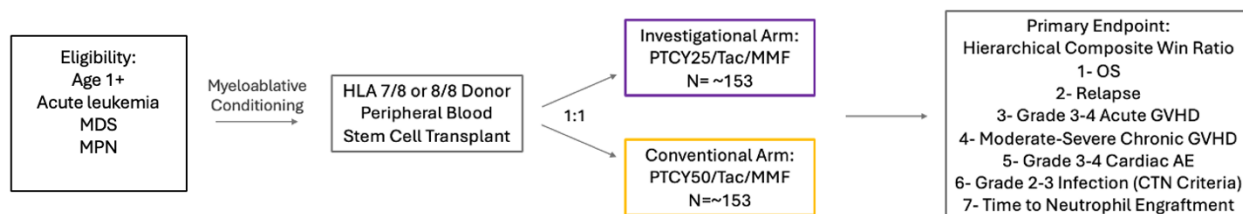
Key safety endpoints for the study are non-relapse mortality and Grade III-IV acute GVHD. The rates of these events by Day 100 post-HCT will be monitored separately for each arm on a daily basis using time-to-event sequential probability ratio tests (TITE-SPRTs). These tests will evaluate the null hypotheses that the Day 100 rates of non-relapse mortality and Grade III-IV acute GVHD do not exceed 5%.

STUDY SCHEMA

BMT CTN 2503 Aims To:

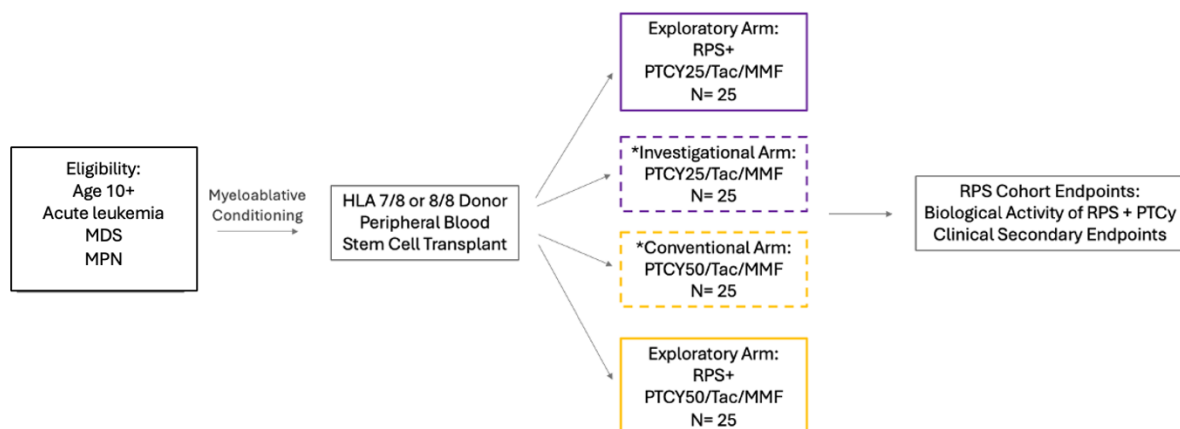
Determine whether PTCy25/Tac/MMF is superior to PTCy50/Tac/MMF as determined by the WIN Ratio
AND generate prospective multicenter data on a Microbiome Intervention in combination with PTCy

Main Study Schema



*~25 patients included in the investigational arm and ~25 patients included in the conventional arm will come from the RPS substudy

RPS Substudy Schema



*~patients enrolled into the hatched line (non RPS) groups will be counted towards the total N of the main study and included in the primary endpoint