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

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PROTOCOL SYNOPSIS

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

Co-Principal Investigators: Zachariah DeFilipp, MD and Elizabeth Hexner, MD

Study Design: The study is designed as a randomized, Phase III, open label multicenter trial comparing two acute graft-versus-host disease (aGVHD) prophylaxis regimens: investigational tacrolimus/ methotrexate/ ruxolitinib (Tac/MTX/Rux) versus post-transplant cyclophosphamide/ tacrolimus/ mycophenolate mofetil (PTCy/Tac/MMF) in the setting of non-myeloablative/reduced intensity conditioning (RIC) allogeneic peripheral blood stem cell (PBSC) transplantation. The two regimens will be compared for both non-inferiority and superiority.

An initial, randomized, open-label, parallel-cohort run-in phase will be used to evaluate two doses of ruxolitinib when used in combination with Tac/MTX to select the dose that will be used in the randomized Phase III portion.

Primary Objective: The primary objective of the Phase III portion of the trial is to compare GVHD-free survival (GFS) up to 24 months after hematopoietic cell transplantation (HCT) between the two GVHD prophylaxis regimens. An event for this time-to-event outcome is defined as Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression, or death by any cause.

Secondary Objective: Secondary objectives are to describe for each treatment arm rates of Grade II-IV and III-IV acute GVHD, rates of NIH mild, moderate, and severe chronic GVHD, hematologic recovery (neutrophil and platelet), lymphocyte recovery, proportion of participants with full or mixed donor chimerism or graft rejection, disease relapse or progression, non-relapse mortality, incidence of biopsy-confirmed post-transplant lymphoproliferative disorders (PTLD), incidence of infections, GVHD-free, relapse-free survival (GRFS), graft failure, toxicity, disease-free survival, overall survival, and patient reported outcomes (PRO).

Eligibility Criteria: Eligible participants are at least 18.0 years of age undergoing allogeneic PBSC transplant for the treatment of acute leukemia or chronic myelogenous leukemia with no circulating blasts and with less than 5% blasts in the bone marrow; or myelodysplasia/chronic myelomonocytic leukemia with no circulating blasts and with less than 10% blasts in the bone

marrow; follicular lymphoma, Hodgkin lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma and anaplastic large cell lymphoma sensitive to chemotherapy who are eligible for an allogeneic HCT. Participants are eligible only if receiving a RIC regimen.

Participants must have a related or unrelated PBSC donor. Sibling donor must be a 6/6 match for HLA-A and HLA-B at intermediate or higher resolution, and -DRB1 at high resolution using DNA-based typing; must be willing to donate peripheral blood stem cells; and meet institutional criteria for donation. Unrelated donor must be a 7/8 or 8/8 match at HLA-A, -B, -C, and -DRB1 at high resolution using DNA-based typing; must be willing to donate PBSCs; and be medically eligible to donate stem cells according to NMDP criteria.

Treatment Description: Following optimal dose determination during the run-in phase, participants will be randomized to receive one of two specified GVHD prophylaxis regimens: Tac/MTX/Rux or PTCy/Tac/MMF.

Tac/MTX/Rux: Tacrolimus will begin on Day -3. MTX will be administered on Day +1, +3, and +6. Ruxolitinib will begin starting Day -1 and continue through Month 12, followed by a taper. The starting dose of Ruxolitinib will be 5 mg or 10 mg twice daily, as determined by the randomized, dose finding run-in phase of the trial.

PTCy/Tac/MMF: PTCy will be given on Days +3 and +4, followed by Tac/MMF starting on Day +5.

Accrual Objective: The clinical trial will enroll 572 participants, with 50 participants for the dose-finding run-in and 261 per arm after the dose-finding run-in.

Accrual Period: The estimated accrual period is 48 months.

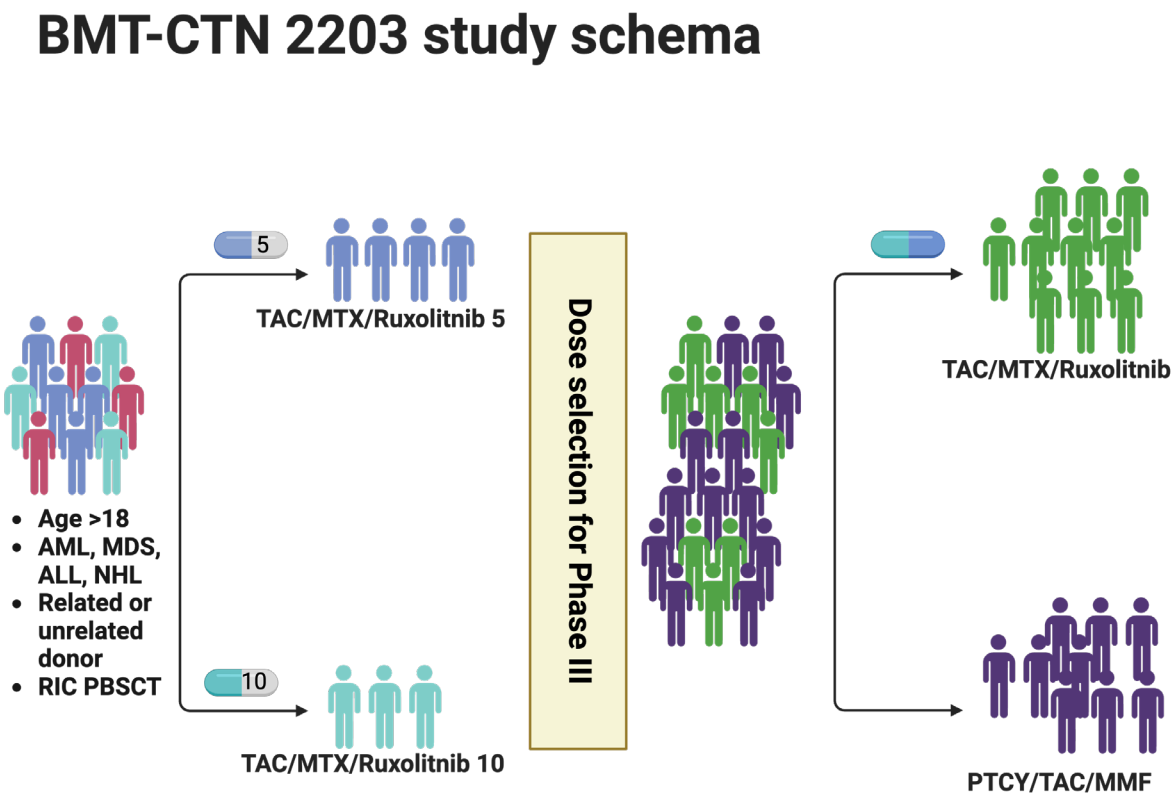
Study Duration: Participants will be followed for 24 months post-PBSC transplant.

Stopping Guidelines: Monitoring of three key safety endpoints (overall mortality by 100 days post-HCT, primary graft failure by Day 28 post-HCT, Suspected Unexpected Serious Adverse Reaction (SUSARs) by Day 28 will be conducted, and if any rate significantly exceeds pre-set thresholds, the NHLBI will be notified in order that the Data and Safety Monitoring Board (DSMB) can be advised. The stopping guidelines serve as a trigger for consultation with the

DSMB for additional review and are not formal “stopping rules” that would mandate automatic closure of study enrollment.

Correlative Studies: Immune reconstitution will be collected for participants on both arms at specified timepoints.

Outline of Treatment Plan



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CHAPTER 1

1 BACKGROUND AND RATIONALE

1.1 Introduction

1.1.1 Introduction to GVHD

Graft-versus-host disease (GVHD) is an important cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). GVHD occurs when immunocompetent T cells in the donated tissue (the graft) recognize the recipient (the host) as foreign. The resulting immune response activates donor T cells and other donor-derived immune cells, which attack the recipient to eliminate foreign antigen-bearing cells.[1, 2] This process can lead to extensive tissue damage and potential organ failure in the HCT recipient.[3]

There are two main clinical presentations of the disease: acute GVHD and chronic GVHD. Acute GVHD typically occurs in the early months after allogeneic HCT. Signs of typical acute GVHD are limited to three organs: skin (maculopapular rash), gastrointestinal tract (nausea, vomiting, and anorexia; and watery or bloody diarrhea and crampy abdominal pain), or liver (hyperbilirubinemia with jaundice due to damage to the small bile ducts).[1] The diagnosis of acute GVHD relies on the assessment of target organs by means of clinical and laboratory analyses and potential biopsy. The severity is graded clinically by tabulating the extent of the involvement of the three main target organs.[4, 5] Chronic GVHD typically occurs in the later months after allogeneic HCT and is a major determinant of quality of life, morbidity, and mortality in long-term HCT survivors. Chronic GVHD can involve the tissues targeted in acute GVHD (skin, gastrointestinal tract, liver), but can also involve numerous other organ systems, including mouth, esophagus, eyes, lung, joint and fascia, and genital tract, among others.[6] Like acute GVHD, the diagnosis of chronic GVHD also relies on the assessment of target organs by means of clinical and laboratory analyses and potential biopsy. The NIH consensus criteria provide a framework to score the severity of chronic GVHD, with each organ system being evaluated individually for severity and the individual scores being added to calculate an overall severity of chronic GVHD (mild, moderate, or severe).[6]

Corticosteroids remain as the first-line systemic treatment for both acute GVHD and chronic GVHD. In recent years, the treatment landscape for the disease has expanded tremendously, with four US Food and Drug Administration (FDA) approvals for GVHD treatment since 2017.[7] Despite these therapeutic advancements, strategies that minimize the incidence of acute and chronic GVHD, without other adverse effects including increased risk of relapse, remain of utmost importance to improve outcomes for allogeneic HCT recipients.

1.1.2 Introduction to GVHD Prophylaxis

Significant progress has been made in the development of immunosuppressive GVHD prophylaxis regimens.[8] After early transplants were performed with methotrexate (MTX) or cyclosporine (CSA) as single-agent GVHD prophylaxis, randomized studies established the combined use of MTX and CSA to be superior to single-agent approaches.[9] Tacrolimus (Tac) in combination with MTX showed reductions in acute GVHD compared to CSA/MTX and became a commonly used regimen after randomized trials in the related and unrelated donor settings.[10, 11] Numerous alternative approaches to preventing GVHD have been investigated, but have failed to significantly improve transplant outcomes.[12] Thus, for many years, Tac/MTX remained as the standard of care for acute GVHD prophylaxis for many transplant centers, despite its historically limited efficacy, with 40-60% of recipients developing Grade II-IV acute GVHD.

More recently, post-transplant cyclophosphamide (PTCy), given in combination with Tac and mycophenolate mofetil (MMF), emerged as a novel approach to GVHD prophylaxis.[13] Already adopted as the standard immunosuppressive strategy for haploidentical related donor transplantation, two randomized trials preliminarily investigated the broader application of PTCy to allogeneic HCT. One trial, a multicenter, Phase II study BMT CTN 1203, randomized 273 participants (1:1:1) to one of three GVHD prophylaxis regimens: PTCy/Tac/MMF, Tac/MTX/bortezomib, and Tac/MTX/maraviroc. The primary endpoint was GVHD-free, relapse-free survival (GRFS), a standard composite endpoint defined as Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression, disease relapse or progression, or death by any cause. PTCy/Tac/MMF was the only investigational arm to result in improved GRFS as compared to a contemporaneous non-randomized prospective cohort of 224 participants receiving Tac/MTX (Hazard Ratio (HR) 0.72, 90% CI 0.54-0.94, p=0.04).[14] The other major trial of PTCy was a multicenter, Phase III HOVON-96 trial, where 160 participants were randomized 1:2 between conventional GVHD prophylaxis with CSA/MMF or PTCy/CSA in the setting of HLA-matched related or unrelated allogeneic HCT. PTCy/CSA resulted in lower rates of acute and chronic GVHD without affecting relapse, resulting in an improved one-year estimate of GRFS (45% vs 22%).[15] Together, these promising studies supported the expanded use of PTCy-based immunosuppression beyond haploidentical transplantation, and formed the basis for BMT CTN 1703 protocol.

1.1.3 BMT CTN 1703

Building upon the promising Phase II results of BMT CTN 1203, a large randomized, Phase III, multicenter trial (BMT CTN 1703) was conducted to compare PTCy/Tac/MMF to Tac/MTX in the setting of non-myeloablative/reduced intensity conditioning (NMA/RIC) allogeneic HCT with peripheral blood stem cells (PBSC). A total of 431 participants were enrolled. Eligible adults with hematologic malignancies undergoing RIC allogeneic HCT with a 6/6 matched related (n=128), 8/8 matched unrelated (n=288), or 7/8 single mismatch (n=15) peripheral blood stem cell donor were randomized 1:1 to receive PTCy/Tac/MMF (n=214) or Tac/MTX (n=217). Like BMT CTN 1203, the primary endpoint of the study was GRFS. The primary hypothesis was that PTCy/Tac/MMF would have a ≥15% higher GRFS at 1 year than Tac/MTX in the intent-to-treat population. The results of the trial were recently reported.[28] The two study arms were well balanced by patient sex, age, Karnofsky performance status, disease risk, comorbidities, donor match, conditioning regimen, and post-transplant maintenance therapy. In the multivariate Cox regression model of the primary endpoint, the PTCy treatment group had a significantly lower hazard of GRFS than Tac/MTX (HR 0.641, 95% CI: 0.492 to 0.835, p=0.001). The adjusted 1-year GRFS rate was 52.7% (95% CI: 45.8%, 59.2%) for the PTCy arm, and 34.9% (95% CI: 28.6%, 41.3%) for the control arm. The lower proportion of GRFS events in the PTCy arm was driven by a reduction in both acute and chronic GVHD. The Day 100 Grade III-IV acute GVHD was 6.3% versus 14.7% (p=0.001), and chronic GVHD rate at 1 year was 21.9% versus 35.1% (p=0.005) for PTCy versus Tac/MTX, respectively. There was no difference in the relapse/progression rate at 1 year (20.8% versus 20.2%, p=0.9), or overall survival (OS) (76.8% versus 72.6%, p=0.3), in PTCy versus Tac/MTX. Grade 3 infection rates were similar between the arms (12.2% for PTCy versus 13.3%, p=0.8) but Grade 2 infections were greater for PTCy (33.7% versus 23.5%, p=0.002). There was no difference in cytomegalovirus (CMV) reactivation between the treatment arms (7.3% for PTCy versus 7.1%, p=0.8).

Thus, BMT CTN 1703 met its primary endpoint, demonstrating a higher 1-year GRFS with PTCy/Tac/MMF compared to Tac/MTX, owing to significant improvements in GVHD risk without increased risk of relapse or death. The results of this trial suggest that PTCy/Tac/MMF should be adopted as the standard of care for GVHD prophylaxis in the setting of related and unrelated allogeneic PBSC NMA/RIC HCT.

1.1.4 Introduction to Ruxolitinib

Ruxolitinib is a potent, selective, orally available inhibitor of Janus kinases (JAKs) JAK1 and JAK2, with modest to marked selectivity against TYK2 (tyrosine kinase 2) and JAK3, respectively. JAKs are non-receptor tyrosine kinases that mediate signaling of a number of cytokines and growth factors important for both hematopoiesis and the immune response. Ruxolitinib was first developed to treat myeloproliferative neoplasms (MPN), myeloid malignancies driven by dysregulation of the JAK pathway. Ruxolitinib is approved for the treatment of two MPN subtypes: myelofibrosis (MF) and polycythemia vera. Surprisingly, rather than a specific reduction in the JAK2 mutant clone in MPN (predominantly driven by $JAK2^{V617F}$), ruxolitinib appeared to be active at least in part via modification of the immune milieu, including the cytokine environment. [21] Cytokine modification and an apparent selective preservation of regulatory T cells (Tregs) and induction of immune tolerance led to preclinical studies in GVHD, and some early reports of effective treatment of steroid refractory (SR) GVHD. [22,23] These strong pre-clinical data showing that inhibition of JAK1/2 signaling results in reduced proliferation of donor immune cells, suppression of adverse cytokines in response to recipient antigens, as well as impairment of antigen presenting cells in vitro and in vivo were encouraging.[16] In vivo JAK 1/2 inhibition by ruxolitinib improved survival of mice in an established GVHD model incorporating human immune cells, and impaired differentiation of GVHD relevant T-cell subsets.[16] The role for JAK-inhibition in GVHD was initially confirmed with data from a retrospective case series of patients with SR acute and chronic GVHD treated off-label with ruxolitinib, demonstrating that the majority of patients responded to ruxolitinib treatment.[17]

These preclinical and clinical observations formed the basis for multiple large prospective clinical trials that established ruxolitinib as an effective agent in the treatment of both SR acute and chronic GVHD. Based on these studies, the FDA approved ruxolitinib for the treatment of SR acute GVHD and SR chronic GVHD.

REACH1: Ruxolitinib is active in SR GVHD

REACH1 was a multicenter Phase II trial which accrued participants at 26 medical centers in the United States.[18] Eligible participants included those who were at least 12 years of age with Grade II-IV SR GVHD per MAGIC criteria,[5] and receipt of < 2 prior lines of systemic therapy for GVHD other than corticosteroids. Steroid refractory criteria included participants who had progressive GVHD after 3 days of primary treatment or lack of improvement after 7 days of treatment with equivalent of at least 2 mg/kg methylprednisolone, inability to taper corticosteroids, or development of newly involved organ system after initiation of low-dose corticosteroid treatment. The primary endpoint was 28-day overall response rate (ORR), which was defined as a complete response (CR), very good partial response (VGPR), or partial response (PR).

Ruxolitinib was given orally at a dose of 5 mg twice daily, with optional increase to 10 mg twice daily in the absence of cytopenia. A total of 71 participants received at least one dose of ruxolitinib. The median age was 58 years and most participants (n = 48, 67.6%) had Grade III-IV acute GVHD at enrollment. The median average total daily dose of ruxolitinib was 10.3 mg/day (range: 5-20) and the median duration of treatment was 46 days (range: 4-473). The most common reasons for treatment discontinuation were adverse events (AEs) (28.2%), investigator discretion (28.2%), and death (9.9%). Only 8.5% of participants discontinued treatment for acute GVHD progression. More than half of participants (54.9%) had a response at Day 28, including 26.8% who experienced a CR. The median duration of response (DOR) was 345 days after ruxolitinib initiation. The ORR at any time for the entire cohort was 73.2%, including four participants who responded after Day 28 (1 CR, 3 PR). The only significant association with response in subgroup analysis was GVHD grade at enrollment, as participants with Grade II GVHD had higher ORR compared to Grade III and IV (82.6% versus 41.2% versus 42.9%). Indeed, there was a

correlation in CR rate from participants with baseline Grade II GVHD (47.8%) to Grade III (20.6%) and Grade IV (7.1%). The median OS was 7.6 months, with 6- and 12-month OS rates of 51% and 42.6%, respectively. The 6-month cumulative incidence rate for non-relapse mortality (NRM) was 44.4% (95% CI, 32.5%-55.7%) and the 12-month cumulative rate for NRM was 52.9% (95% CI, 39.6%-64.5%) and both were lower for Day 28 responders. Of note, and relevant to the composite endpoint for this BMT CTN 2203 study, only four participants were reported to have developed chronic GVHD after treatment with ruxolitinib.

Every participant enrolled into the study experienced at least one treatment emergent adverse event (TEAE) and 74.6% experienced at least one treatment-related adverse event (TRAE) with the most common being thrombocytopenia (Any grade: 47.9%, Grade 3 or 4: 42.3%), anemia (Any grade: 35.2%, Grade 3 or 4: 28.2%), and decreased neutrophil count (Any grade: 26.8%, Grade 3 or 4: 21.1%). This generally manageable myelosuppression is felt to be related to direct JAK2 on-target inhibition of hematopoiesis. Other AEs experienced by at least 10% of participants included decreased white blood count (Any grade: 19.7%, Grade 3 or 4: 11.3%) and alanine aminotransferase (ALT) elevation (Any grade: 11.3%, Grade 3 or 4: 1.4%). Toxicity led to ruxolitinib discontinuation, dose reduction, and treatment interruption in 32.4%, 35.2%, and 40.8% of participants, respectively. Grade 5 AEs were experienced by two participants (pulmonary hemorrhage and sepsis, both n = 1).

REACH 2: Ruxolitinib is superior to standard therapy in SR GVHD

The compelling results of the single arm REACH1 trial were further confirmed by REACH2, a randomized international multicenter Phase III trial comparing ruxolitinib versus investigators choice for therapy of SR acute GVHD.[19] Key eligibility criteria mirrored those for REACH1 as described above including participants with Grade II-IV SR acute GVHD who had received at most one prior systemic therapy other than steroids for acute GVHD. The primary endpoint was Day 28 ORR and the key secondary endpoint was DOR at Day 56.

A total of 309 participants were randomized from April 2017 until May 2019, with 154 participants receiving ruxolitinib orally at a dose of 10 mg twice daily. The median age of enrolled participants was 54.0 years. The most common initial control treatment was extracorporeal photopheresis (27%).

REACH 2 found that participants who received ruxolitinib had significantly higher Day 28 ORR compared to the control group (62% versus 39%; Odds Ratio [OR] :2.64, $p < 0.001$) and were more likely to experience a CR (34% versus 19%). Participants with Grade II GVHD were most likely to experience an objective response in both groups (ruxolitinib: 75%; control group: 51%). Participants with Grade IV GVHD receiving ruxolitinib were more than twice as likely to have a response compared to the control group (53% versus 23%; OR:3.76). The DOR at 56 days was also significantly higher in the ruxolitinib group compared to the control group (40% versus 22%; OR:2.38, $p < 0.0001$) and the best overall response at Day 28 was 82% in the ruxolitinib group and 61% in the control group (OR:3.07, 95% CI: 1.80 to 5.25). Median OS and failure-free survival (FFS) also favored ruxolitinib (OS: 11.1 vs. 6.5 months, HR:0.83, 95% CI: 0.60-1.15; FFS: 5.0 versus 1.0 months, HR:0.46; 95% CI: 0.35 to 0.60).

Safety was similar to REACH1: all participants who received ruxolitinib (95%) experienced at least one AE, with 78% experiencing Grade ≥ 3 AEs. Hematologic laboratory abnormalities were noted with similar frequency as in REACH1 with thrombocytopenia (Any grade: 50%, Grade ≥ 3: 41%), anemia (Any grade: 30%, Grade ≥ 3: 22%), and neutropenia (Any grade: 16%, Grade ≥ 3: 13%) being the most common. Other AEs observed in ≥ 10% of participants included cytomegalovirus infection, peripheral edema, hypokalemia, hypertension, hypoalbuminemia, pyrexia, and hypomagnesemia. Adverse events that led to a dose modification occurred in 38% of participants treated and 11% of participants discontinued ruxolitinib due to AEs.

REACH3: Ruxolitinib for chronic GVHD

Ruxolitinib was also recently granted FDA approval for SR chronic GVHD based on results from a Phase III, randomized, open label control trial of ruxolitinib at a dose of 10 mg twice daily versus investigator's choice for SR chronic GVHD.[20] Participants were enrolled onto this international trial at 49 centers including the United States, Canada, Australia, and 25 countries in Europe and Asia. Eligible participants were ≥ 12 years of age who had undergone allogenic HCT and subsequently developed moderate-to-severe SR or steroid-dependent chronic GVHD per NIH consensus criteria. Participants were excluded if they received two or more systemic therapies for chronic GVHD in addition to steroids. Participants who had previously received a JAK inhibitor for acute GVHD were eligible if they met the following criteria: (1) had a PR or CR prior to JAK inhibitor treatments and (2) JAK inhibitor had been discontinued at least 8 weeks prior to enrollment onto the trial. The primary endpoint was objective response at 24 weeks, defined as a CR or PR per NIH criteria.

In total, 329 participants were randomized. Most participants (61.1%) were male, and the median age was 49 years. More than half (56.5%) had severe disease, while 42.9% had moderate disease. The most common investigator choice agents used as control therapy were extracorporeal photopheresis (ECP) (34.8%), mycophenolate mofetil (22.2%), and ibrutinib (17.1%). The ORR at 24 weeks was significantly higher in the ruxolitinib group compared to best available therapy (49.7% versus 25.6%, $p < 0.001$). More participants in the ruxolitinib group had a CR compared to the control therapy group (6.7% versus 3.0%). The best overall response was also significantly higher in the ruxolitinib group compared to the control group (76.4% versus 60.4%, $p = 0.001$). Participants receiving ruxolitinib also had longer FFS (> 18.6 versus 5.7 months, $P < 0.001$) compared to the control group. The ruxolitinib group was more likely to discontinue treatment for toxicity (17.0% versus 4.9%) and less likely to discontinue for lack of efficacy (14.5% versus 42.7%).

Similar to REACH1 and REACH 2, common AEs were anemia (29.1%), thrombocytopenia (21.2%), and neutropenia (10.9%). Other AEs experienced by > 10% of participants were pneumonia (10.9%), diarrhea (10.3%), ALT elevation (15.2%), elevated creatinine (13.9%), hypertension (15.8%), pyrexia (15.8%), cough (10.3%), and fatigue (10.3%).

1.2 Tacrolimus/Methotrexate/Ruxolitinib (Tac/MTX/Rux) for GVHD prevention

The encouraging results from treatment studies of acute and chronic GVHD and the mechanism of action of ruxolitinib led to the hypothesis that ruxolitinib would be safe and effective in preventing GVHD. Despite the extensive clinical experience with ruxolitinib in the setting of GVHD treatment, the role of JAK inhibition as a GVHD prophylaxis approach had only preliminarily been evaluated. To this end, two ongoing multicenter Phase II studies are evaluating safety and efficacy of ruxolitinib in the GVHD prophylaxis setting. In NCT03286530, participants aged ≥ 60 with acute myeloid leukemia (AML) in first complete remission received ruxolitinib continuously in 28-day cycles, starting between Day 30-90 after HCT, for up to 24 cycles. In NCT03427866, participants with primary or secondary MF received ruxolitinib prior to, during, and after HCT for up to 13 cycles after HCT. An interim analysis of the combined AML and MF cohort who had reached at least one year post transplant was recently presented. Fifty-four participants (AML, n = 33; MF, n = 21) were treated; the median age at HCT was 67 years (range, 46-79). Hematopoietic cell transplantations were performed with matched unrelated donors (MUD) (n = 42), MSD (n = 11), or mismatched unrelated donor (MMUD) (n = 1). All conditioning regimens were reduced intensity using PBSC grafts and addition of ruxolitinib to standard tacrolimus/methotrexate GVHD prophylaxis. The median follow-up among survivors was 18 months (range, 7-43). In the AML cohort, the median start date of ruxolitinib after HCT was Day +47 (range, 32-93). The median number of cycles received was 19 (range, 1-24) and 26 of the 33 AML patients had completed or

were off treatment. In the MF cohort, the median number of cycles received was 12 (range, 2-13). As in the treatment studies of acute and chronic GVHD, the most common treatment-related Grade ≥ 3 or higher AEs observed thus far were anemia (n = 10), neutropenia (n = 5), and thrombocytopenia (n = 5). In the entire group, the 6-month cumulative incidence of Grade II-IV acute GVHD was 24% (95% CI: 14-36), with no cases of Grade III-IV observed. Notably, in the AML study, 5 of the 6 GVHD cases occurred prior to initiation of post-HCT ruxolitinib. There were no cases of emergent Grade III or IV acute GVHD in the study, including no severe lower GI GVHD. While the 12-month incidence of all cases of chronic GVHD was 21% (95% CI: 11-33), the 12-month incidence of moderate-severe chronic GVHD requiring systemic therapy was remarkably low, at 3.8% (95% CI: 0.7-12). The 18-month cumulative incidence of NRM was 8% (95% CI: 2.5-18), with only one death attributed to GVHD. The 18-month cumulative incidence of disease relapse was 24% (95% CI: 13-37). The 18-month OS and GRFS were 79% (95% CI: 64-88) and 67% (95% CI: 52-78), respectively. The 18-month GVHD-free survival (GFS) was 76% (95% CI: 62-86).

Additional promising studies are published or ongoing, demonstrating the feasibility and activity of ruxolitinib to improve post-transplant outcomes and prevent GVHD. Summarized in Table 1.2A, multiple studies have shown no apparent adverse impact on engraftment and appear to consistently show low rates of GVHD.

In summary, the use of prolonged post-HCT ruxolitinib appears feasible and is associated with low rates of emergent severe acute and chronic GVHD. Based on these studies, comparative trials of ruxolitinib for GVHD prophylaxis are warranted.

Table 1.2A: Previous Studies on Ruxolitinib Use for GVHD Prophylaxis

Study	Disease	n=	Cond	Ppx	Ruxolitinib start	Dose 1	Dose 2	Treatment duration	Dose Interruptions	ANC >500 Median (range)	Graft failure (Yes/No)	GVHD II-IV	GVHD III-IV	OS%
Kröger N BBMT 2018[24]	MF	12	Flu (30 x 5)/Bu (0.8 x 10)	ATG/ CsA/ MMF	Pre/start of conditioning	5 BID (until Day+20/eng)	5 QD (Day +21-28)	Off Day +29	16% (cytopenias, Day 17, 18)	12 (11-18)	No	42%	8%	100 (17M)
Salit RB preliminary data[25] *(unpublished)*	MF	22	Flu Mel (16) Bu/Cy (6)	Tac/ MTX (10x4)	8+w pre	Decrease to 5 BID on Day -4	10 BID on Day +28 if counts tolerate	9-12 months post HCT	18% (cytopenias, LFTs)	20 (15-26)	No	25%	12%	100 (1Y)
Ali H, Blood Adv 2022[26]	MF	18	Flu/Mel	Tac/Rap	Continue or Day-3	5 or 10 BID (until Day+30)	Rapid taper	Off Day +35	1 mucositis	17 (12-23)	No	17% Day +100	11% Day +100	77 (1Y)
DeFilipp Z, TCT 2022[27]	AML/ MF	54	Flu/Mel (37) or RIC Flu/Bu (17)	Tac/MTX (5x3)	AML: start Day +30-90; MF: start Day -14	MF: start at 5 mg BID, decrease to 5 mg daily on Day -1 when fluc started	AML: starting dose is 5 mg BID (if fluc) or 10 mg BID (if no fluc)	MF: for 12 cycles AML: for 24 cycles	N/A	MF only 14 (11-24)	No	24%	0%	79 (18M)

Abbreviations: AML= acute myeloid leukemia; ATG= antithymocyte globulin; Bu= Busulfan; CsA= cyclosporine; Flu= fludarabine; MAC=myeloablative conditioning; Mel= melphalan; MF= myelofibrosis; MMF= mycophenolate mofetil; MTX= methotrexate; Ppx= prophylaxis; Rap= rapamune; RIC= reduced intensity conditioning; Tac= Tacrolimus; Fluc= fluconazole.

1.3 Rationale for Ruxolitinib Dose Finding

While higher doses of ruxolitinib are commonly used in the non-transplant management of myelofibrosis, the two doses of 5 mg and 10 mg twice daily have been explored in the peri-transplant setting and in the setting of GVHD treatment. Both doses appear feasible without adverse impact on neutrophil engraftment in the peri-transplant period in myelofibrosis (Table 1.2A) but the optimal dose has not been established in the prevention setting across hematologic malignancies. Of note, in a pilot open-label study of peri-transplant ruxolitinib for participants with myelofibrosis investigating those doses of 5 mg and 10 mg twice daily, the recommended phase II dose was 10 mg twice daily and dose-dependent pharmacokinetic and cytokine profile seems to favor the 10 mg twice daily dosing.[26] Nonetheless, a formal comparison of ruxolitinib dosing is warranted prior to proceeding to a randomized phase III evaluation of Tac/MTX/Rux prophylaxis.

Thus, an initial, randomized, open-label, parallel-cohort run-in phase will be used to evaluate these two doses of ruxolitinib (5 mg and 10 mg twice daily) when used in combination with Tac/MTX and select the dose that will be used in the randomized Phase III portion.

1.4 Rationale for a Randomized Trial

This randomized, multicenter Phase III clinical trial will evaluate two GVHD prophylaxis approaches for their efficacies in improving the proportion of participants with GFS up to 24 months, defined as those who do not develop Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression, or death by any cause. The two approaches to be investigated will be investigational Tac/MTX/Rux and PTCy/Tac/MMF which will serve as the control arm.

The primary endpoint for this trial will be GFS up to 24 months. Events for this time to event outcome will be defined as any of the following: 1) Grade III-IV acute GVHD, 2) chronic GVHD requiring systemic immune suppression, or 3) death by any cause.

Given the superiority of PTCy/Tac/MMF to Tac/MTX in the prevention of acute and chronic GVHD in BMT CTN 1703, the current open label trial design was chosen over a randomized, Phase III, placebo-controlled trial comparing Tac/MTX/Rux to Tac/MTX/Placebo. The current trial design has co-primary objectives to establish non-inferiority and/or superiority of Tac/MTX/Rux compared to PTCy/Tac/MMF. While the results of BMT CTN 1703 represent significant progress in preventing GVHD, engraftment (neutrophils, platelets, lymphocytes) was significantly delayed, as were the risk of Grade II-III infections in the PTCy/Tac/MMF arm of the trial. These differences highlight opportunities for improving outcomes using the Tac/MTX backbone with respect to GVHD, infection and engraftment. Results for study outcomes from BMT CTN 1203, BMT CTN 1703, the Tac/MTX/Rux Phase II trials (TCT meeting 2022) are outlined in Table 1.3A. The trial design is powered to detect superiority of the investigational arm (Tac/MTX/Rux) compared to the newly established standard (PTCy/Tac/MMF) for a true HR of 0.65 and is also powered to establish non-inferiority of the investigational arm (Tac/MTX/Rux) to PTCy/Tac/MMF, when the true HR is 0.73. Documentation of the appropriate non-inferiority margin that preserves 50% of the treatment effect of PTCy/Tac/MMF vs. Tac/MTX is provided in Section 5.2.

Table 1.3A: Clinic outcomes of PTCy/Tac/MMF, Tac/MTX, and Tac/MTX/Rux in the setting of HLA-matched RIC allogeneic PBSC

Study	Regimen	Total participant	12-month Outcomes							
			Gr II-IV aGVHD	Gr III-IV aGVHD	cGVHD	NRM	Relapse	OS	GRFS	GFS
BMT CTN 1203	PTCy/Tac/MMF	92	27% (20,35)	2% (0,5)	28% (20,36)	11% (6,17)	28% (21.37)	71% (63,78)	43% (34.54)	N/A
BMT CTN 1203	Tac/MTX	224	30% (25,36)	13% (9,16)	38% (33,43)	16% (12, 21)	25% (20,29)	71% (66,76)	34% (28,40)	N/A
BMT CTN 1703	PTCy/Tac/MMF	214	54% (47,60)	6% (4,10)	22% (16,28)	12% (8, 17)	21% (16, 26)	77% (70,82)	52% (45,59)	62% (55,68)
BMT CTN 1703	Tac/MTX	217	52% (45,59)	15% (10,20)	35% (29,42)	17% (12,22)	20% (15,26)	73% (66,78)	35.5% (29,42)	45% (38,52)
DeFilipp Z, TCT 2022[27]	Tac/MTX/Rux	54	24% (14,36)	0%	21% (11,33)	6% (2.14)	19% (10,31)	87% (74,94)	71% (57,82)	81% (68,89)

CHAPTER 2

2 STUDY DESIGN

2.1 Study Overview

The BMT CTN 2203 study is a Phase III randomized, open label, multicenter trial comparing investigational Tac/MTX/Rux versus PTCy/Tac/MMF for GVHD prophylaxis in participants with controlled malignant diseases receiving an allogeneic PBSC transplant after an NMA/RIC regimen. The primary endpoint is GFS up to 24 months.

Given that the majority of Phase II data using ruxolitinib in the peri-transplant (pre- and early post-transplant) period is in patients with myelofibrosis undergoing transplant and with limited investigation into ruxolitinib dosing, an initial dose finding run-in phase will evaluate the safety and efficacy of two doses of ruxolitinib when used in combination with Tac/MTX and select the dose that will be used in the randomized Phase III portion.

2.1.1 Dose Finding Run-in Phase

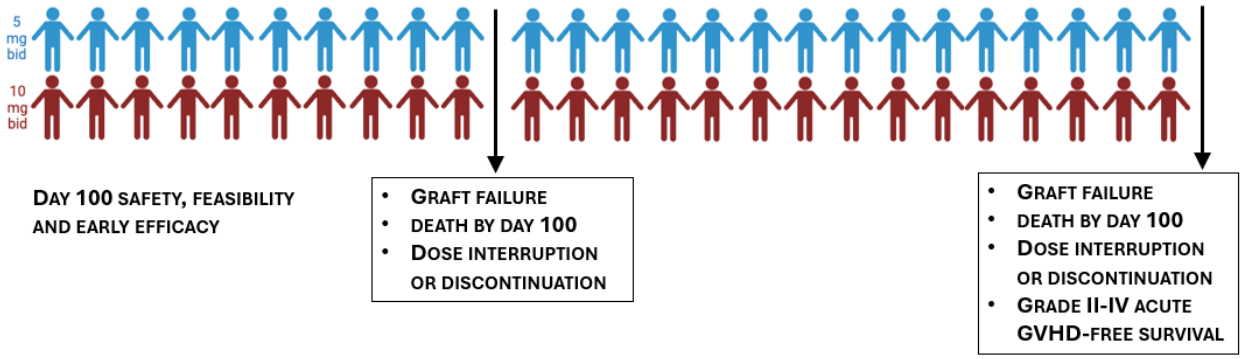
The dose finding run-in will employ a randomized, open-label, parallel-cohort design to further explore dose, feasibility and preliminary efficacy in this population to select a dose of ruxolitinib for the randomized phase III study. The run-in will randomize 25 participants to one of two dosing cohorts of ruxolitinib (5 mg twice daily or 10 mg twice daily) as noted in Table 2.1A. After enrollment of 50 participants (25 to each dose cohort) and confirmation of receipt of dosing, enrollment will be closed until the starting dose for the phase III population is defined.

After 10 participants are enrolled on each arm and reach Day 100, the following will be reviewed:

- Key safety endpoints: graft failure by Day 28 and mortality by Day 100
- Key feasibility endpoint: proportion of participants requiring dose reduction or interruption.

Additional analyses of safety and efficacy data will be conducted once all run-in participants have been followed for 100 days.

- Key efficacy endpoint: Grade II-IV acute GVHD-free survival by Day 100 as a short-term measure of activity.
- Safety endpoints include serious adverse events (SAE) in the first 100 days, grade 2-5 AEs, and infections.



All run-in patients will continue as such:

- Participants will receive a reduced intensity or non-myeloablative conditioning regimen as specified in Section 2.5.1.
- As outlined in the Treatment Plan and Supportive Care sections (Sections 2.5 and 2.7 respectively), patient will receive the GVHD prophylaxis regimen assigned, and other supportive care as detailed in the protocol.
- Participants will be followed for 24 months post-PBSC transplant, with assessments post-transplant as outlined in Section 4.6, and adverse event reporting as outlined in Section 4.7.

Table 2.1A: Ruxolitinib Dose by Group for Dose-Finding Run-in

Ruxolitinib Dose by Group for Dose-Finding Run-in	
Group 1 **Ruxolitinib 5 mg BID, tacrolimus, and methotrexate**	**Group 2:** **Ruxolitinib 10 mg BID, tacrolimus, and methotrexate**

2.1.2 Main Study Randomized Phase III Portion

Following the dose finding run-in phase, the main study will begin enrollment with an anticipated 522 participants (261 per arm).

- Eligible participants will be randomized to receive one of two specified GVHD prophylaxis regimens: Tac/MTX/Rux (investigational) or PTCy/Tac/MMF (control arm) as noted in Table 2.1B.
- Participants will receive a reduced intensity or non-myeloablative conditioning regimen as specified in Section 2.5.1.
- As outlined in the Treatment Plan and Supportive Care sections (Sections 2.5 and 2.7 respectively), patient will receive the GVHD prophylaxis regimen assigned, and other supportive care as detailed in the protocol.
- Participants will be followed for 24 months post-PBSC transplant, with assessments post-transplant as outlined in Section 4.6, and adverse event reporting as outlined in Section 4.7.

Table 2.1B: Main Study Randomized Groups for Phase III

Group A (investigational): Ruxolitinib*, tacrolimus, and methotrexate *Dose determined by run-in	**Group B (standard): Tacrolimus, mycophenolate mofetil, and cyclophosphamide**
• Ruxolitinib: given initially twice a day as a pill by mouth beginning the day before your transplant. The dose given will be determined by the run-in phase. Participants will continue taking this drug for 12 months after the transplant. After 12 months, the amount of ruxolitinib will slowly decrease and eventually stop. • Tacrolimus: given initially daily as a pill by mouth at a dose of 0.05-0.06 mg/kg/day or intravenously (IV) through the participant's vein at a dose of 0.02-0.03 mg/kg/day, beginning 3 days before your transplant. The amount of tacrolimus will slowly decrease and eventually stop. This process occurs over several months. • Methotrexate: given intravenously (IV) through the participant's vein at a dose of 5 mg/m^2 on 3 different days (Day 1, 3, and 6) after transplant.	• Tacrolimus: given initially daily as a pill by mouth at a dose of 0.05-0.06 mg/kg/day or intravenously (IV) through the participant's vein at a dose of 0.02-0.03 mg/kg/day, beginning on Day 5 after transplant. The amount of tacrolimus will slowly decrease and eventually stop. This process occurs over several months. • Mycophenolate mofetil: The starting dose will be 15mg/kg given daily intravenously (IV) through the participant's vein or as a pill by mouth 3 times a day, beginning on Day 5 after transplant, and will continue for 30 days. • Cyclophosphamide: given intravenously (IV) through the participant's vein at a dose of 50 mg/kg, over 1-2 hours, on Day 3 and Day 4 after transplant.

2.2 Hypothesis and Specific Objectives

2.2.1 Primary Hypothesis

GVHD-free survival (GFS) of Tac/MTX/Rux will be non-inferior and superior to PTCy/Tac/MMF.

2.3 Study Objectives

2.3.1 Primary Objective

The primary objective of the randomized, dose finding portion of the trial is to compare the safety, feasibility, and efficacy of two ruxolitinib doses in the setting of GVHD prophylaxis. In this portion of the study, these three evaluations will be assessed by:

- Safety: graft failure by Day 28 and overall mortality by Day 100
- Feasibility: proportion of participants requiring dose reduction or interruption by Day 100
- Efficacy: Grade II-IV acute GVHD-free survival by Day 100

The primary objective of the randomized Phase III portion of the trial is to compare GFS up to 24 months after HCT between Tac/MTX/Rux versus PTCy/Tac/MMF. There are co-primary objectives of demonstrating non-inferiority and superiority on the primary endpoint of GFS. An event for this time to event outcome is defined as Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression, or death by any cause.

2.3.2 Secondary Objectives

Secondary objectives are the following comparisons between the two treatments in the Phase III portion based on:

- GVHD-free and relapse/progression-free survival
- Rates of NIH mild, moderate, and severe chronic GVHD (defined by the NIH Consensus Conference Criteria)

- Grade II-IV and III-IV acute GVHD per the NIH Consensus Conference Criteria on Acute GVHD Grading by Day +180
- Hematologic recovery including neutrophil engraftment, platelet engraftment, lymphocyte recovery
- Proportion of participants with full (at least 95% or more) or mixed (5.0-94.9%) total donor chimerism or graft rejection (less than 5% total donor chimerism)
- Graft failure
- Disease relapse or progression
- Non-relapse mortality (NRM)
- Toxicity and Infections
- Disease-free survival
- OS
- PRO

2.3.3 Exploratory Objectives

The Exploratory objectives in the Phase III portion are:

- Current additional systemic immunosuppression-free survival
- Immune reconstitution
- Healthcare Utilization
- SR acute and chronic GVHD
- Ruxolitinib pharmacokinetics (PK) characterization

2.4 Participant Eligibility

2.4.1 Inclusion Criteria

1. Age 18.0 years or older at the time of enrollment.
2. Participants undergoing allogeneic HCT for one of the following indications:
    a. Acute leukemia or chronic myelogenous leukemia with no circulating blasts and with less than 5% blasts in the bone marrow. Therapy related myeloid neoplasms are allowed.
    b. Myelodysplasia/chronic myelomonocytic leukemia with no circulating blasts and with less than 10% blasts in the bone marrow (higher blast percentage allowed in MDS due to lack of differences in outcomes with < 5% versus 5-10% blasts in this disease). Therapy related myeloid neoplasms are allowed.
    c. Lymphoma [follicular lymphoma, Hodgkin lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma and anaplastic large cell lymphoma].
3. Planned NMA/reduced intensity conditioning regimen (see eligible regimens in Table 2.5A).
4. Participants must have a related or unrelated PBSC donor as follows:
    a. Sibling donor must be a 6/6 match for HLA-A and -B at intermediate (or higher) resolution, and -DRB1 at high resolution using DNA-based typing and must be

willing to donate peripheral blood stem cells and meet institutional criteria for donation. HLA-matched parents and children may be used as donors.

b. Unrelated donor must be a 7/8 or 8/8 match at HLA-A, -B, -C and –DRB1 at high resolution using DNA-based typing. Unrelated donor must be willing to donate peripheral blood stem cells and meet NMDP criteria for donation.

c. Donor selection must comply with 21 CFR 1271

5. Cardiac function: Left ventricular ejection fraction at least 45%.
6. Estimated glomerular filtration rate greater than 60 ml/min/1.73 m^2 using the 2021 CKD-EPI formula Note: For eligibility, GFR by 2021 CKD-EPI is required. A baseline creatinine clearance by Cockcroft-Gault should be done to establish baseline CrCl for ruxolitinib dosing.
7. Pulmonary function: DLCO corrected for hemoglobin at least 40% and FEV1 predicted at least 50%.
8. Liver function: AST/ALT < 3x ULN; Total bilirubin < 2 mg/dL excluding Gilbert's syndrome or hemolysis.
9. Karnofsky Performance Score of at least 60%.
10. Female participants (unless postmenopausal for at least one year before the screening visit, or surgically sterilized), agree to practice two effective methods of contraception at the same time, or agree to completely abstain from heterosexual intercourse, from the time of signing the informed consent through 15 months post-transplant. Fertility preservation methods will be left to institutional standards.
11. Male participants (even if surgically sterilized), of partners of women of childbearing potential must agree to one of the following: practice effective barrier contraception or abstain from heterosexual intercourse from the time of signing the informed consent through 15 months post-transplant.
12. Plans for the use of targeted small molecule inhibitor post-transplant maintenance therapy must be disclosed upon enrollment and must be used irrespective of the outcome of the randomization. Planned use of investigational maintenance agents is not permitted. Planned hypomethylating agents as maintenance therapy is not permitted.t
13. Voluntary written consent obtained prior to the performance of any study-related procedure that is not a part of standard medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care.

2.4.2 Exclusion Criteria

1. Prior allogeneic transplant.
2. Active CNS involvement by malignant cells.
3. Participants with secondary AML arising from myeloproliferative neoplasms or secondary AML arising from overlap syndromes, including CMML and MDS/MPN syndromes; participants with secondary AML arising from myelodysplastic neoplasm are eligible.
4. Participants with primary, post-Essential Thrombocythemia (post-ET) and post-Polycythemia Vera (post-PV) myelofibrosis.
5. Participants with uncontrolled bacterial, viral, or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment.
6. Active or inadequately treated latent infection with Mycobacterium tuberculosis (i.e., TB).

7. Presence of clinically significant fluid collection (ascites, pleural or pericardial effusion) that interferes with methotrexate clearance or makes methotrexate use contraindicated.
8. Participants seropositive for human immunodeficiency virus (HIV) with detectable viral load. HIV+ participants with an undetectable viral load on antiviral therapy are eligible.
9. Evidence of uncontrolled hepatitis B virus (HBV) or hepatitis C virus (HCV). The study allows:
    a. Positive HBV serology with undetectable viral load and ongoing antiviral prophylaxis to prevent potential HBV reactivation.
    b. Positive HCV serology with quantitative PCR for plasma HCV RNA below the lower limit of detection, with or without concurrent antiviral HCV treatment.
10. Arterial or venous thrombosis including DVT, PE, stroke, and myocardial infarction within six (6) months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia. Catheter-associated DVT is not exclusionary.
11. Female participants who are pregnant (as per institutional practice) or lactating.
12. Participants with a serious medical or psychiatric illness likely to interfere with participation in this clinical study.
13. Participants with prior malignancies except resected non-melanoma skin cancer or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously must be reviewed and approved by the Protocol Officer or Chairs.
14. Planned use of ATG or alemtuzumab in conditioning regimen.
15. Planned use of prophylactic donor leukocyte infusions.
16. Prior use of ruxolitinib.
17. Prior use of immune checkpoint inhibitors (i.e., PD1, PDL1, CTLA4 modulators) within six (6) months prior to conditioning.
18. For participants with 7/8 HLA-matched donors:
    a. Donor specific antibodies (DSAs) directed at the mismatched donor allele.
    b. Any use of desensitization protocols.
19. Treatment with any other Investigational Medicinal Product (IMP) is not allowed while on study treatment. An IMP is defined as medications without any known FDA or EMA approved indications.

2.5 Treatment Plans

2.5.1 Conditioning Regimens

Eligible participants will receive a reduced intensity or non-myeloablative conditioning regimen according to Table 2.5A. In the event of fludarabine shortage, other regimens deemed to be RIC by the transplant center and not included in Table 2.5A should be submitted to the Protocol Coordinator for consideration by the Protocol Chairs and/or Officer.

The participants conditioning regimen must be determined prior to randomization.

Table 2.5A: Conditioning Regimens^

Reduced Intensity Conditioning	Non-myeloablative Conditioning
Fludarabine/Busulfan (Flu/Bu) • Fludarabine (120-180 mg/m^2) • Busulfan (less than or equal to 8 mg/kg PO or 6.4 mg/kg IV)	**Fludarabine/Cyclophosphamide (Flu/Cy)** • Fludarabine (90-120 mg/m^2) • Cyclophosphamide (120 mg/kg or 2250 mg/m^2)
Fludarabine/Melphalan (Flu/Mel) • Fludarabine (120-180 mg/m^2) • Melphalan (100 - 140 mg/m^2)	**Fludarabine/ Cyclophosphamide/TBI (Flu/Cy/TBI)** • Fludarabine (150 mg/m^2) • TBI (200- 400 cGy) • Cyclophosphamide (29-50 mg/kg)

^Addition of antithymocyte globulin or alemtuzumab is not allowed.

Institutional practice may be used for order and days pre transplant for these regimens, but doses must fall within the listed ranges above with the exception of fludarabine. Additional regimens may not be used.

It is recommended that adjusted ideal body weight be used when calculating conditioning regimen chemotherapy doses.

Ideal Body Weight (IBW) Formulas:

Male: IBW = 50 kg + 2.3 kg/inch over 5 feet

Female: IBW = 45.5 kg + 2.3 kg/inch over 5 feet

Adjusted Ideal Body Weight (AIBW) Formula:

AIBW = IBW + [(0.25) x (ABW* - IBW)]

**ABW: Actual Body Weight*

2.5.2 Hematopoietic Stem Cell Transplantation

Mobilized PBSC is the only allowed graft source for participants enrolled in this clinical trial.

Donors will undergo G-CSF mobilization according to local institutional and donor center practices. Peripheral blood stem cells will be collected by apheresis according to local institutional guidelines. Plasma and red cell depletion are allowed for volume reduction or ABO incompatibility but any other form of graft manipulation (including ex-vivo T-cell depletion) is **not** permitted.

The target CD34+ dose is 4-5 x 10^6/kg with a minimum of 2 x 10^6/kg and a maximum 10 x 10^6/kg (actual body weight) $CD34^+$ cells.

Up to two leukapheresis procedures may be performed to obtain the minimum $CD34^+$ cell target. If, after two leukapheresis procedures, fewer than 2 x 10^6/kg $CD34^+$ cells have been collected, transplant centers will have the discretion to continue PBSC cell harvesting or to proceed to bone marrow harvesting to obtain sufficient cells. A third leukapheresis procedure is discouraged. If bone marrow harvesting is needed in order to meet the desired cell dose, the transplant center needs to notify the Protocol Coordinator, in addition to the Protocol Chairs and/or Officer.

If more than 10 x 10^6/kg $CD34^+$ stem cells are collected, the excess will either be discarded or cryopreserved for future use but will not be administered to the participant. Peripheral blood stem

cells will be administered on Day 0 to all participants according to individual institutional guidelines after appropriate processing and quantification has been performed by the local laboratory. If two leukapheresis procedures are performed to obtain the minimum $CD34^+$ cell dose target, the two products must be combined and infused together on one day. Stem cells are administered through an indwelling central venous catheter. Stem cells can be infused fresh or after cryopreservation, according to institutional guidelines.

2.5.3 GVHD Prophylaxis Regimens

2.5.3.1 Tacrolimus/Methotrexate/Ruxolitinib (Investigational)

Tacrolimus

Tacrolimus will be given per institutional practices, orally at a dose of 0.05-0.06 mg/kg/day or intravenously at a dose of 0.02-0.03 mg/kg/day starting on Day –3. The dose of tacrolimus may be rounded to the nearest 0.5 mg for oral formulations. Subsequent dosing will be based on blood levels per institutional guidelines with a suggested range of 5-15 ng/mL. If participants are on medications which alter the metabolism of tacrolimus (e.g., concurrent CYP3A4 inhibitors), the initial starting dose and subsequent doses should be altered as per institutional practices. If starting voriconazole or posaconazole while the participant is receiving tacrolimus, it is suggested per the package insert that tacrolimus is reduced to one third of the original dose. Dose adjustments should ultimately follow institutional practices, as starting dose and dose adjustments based on blood levels also follow institutional practice.

Tacrolimus taper can be initiated at a minimum of 90 days post HCT if there is no evidence of active GVHD. The rate of tapering will be done according to institutional practices with a goal of being off tacrolimus by Day 180 post HCT if there is no evidence of active GVHD.

Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Participants with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 5-10 ng/mL).

Tacrolimus may have interactions with certain foods, such as grapefruit, which should be avoided. Participants should be educated on the importance of avoiding food and beverages made with grapefruit.

Methotrexate

Methotrexate will be administered at the doses of 5 mg/m^2 IV bolus on Days +1, +3, and +6.

Ruxolitinib

The formulation of ruxolitinib for this study will be ruxolitinib IR. The starting dose of ruxolitinib will be determined by the randomized run-in phase. Ruxolitinib will be administered in 28 day cycles starting Day -1 until 12 months post-transplant, followed by a taper. See Section 2.5.4 for dosing, dose adjustments and modifications according to toxicity, and tapering.

The combination of Tac/MTX and ruxolitinib is intended to be a primary prevention measure against the development of acute and chronic GVHD. ***Continuous dosing*** of ruxolitinib starting on Day -1 is the goal. Given the low incidence of clinically significant chronic GVHD observed in the Phase II clinical trials of Tac/MTX/Rux, the ruxolitinib intervention will be continued until 12 months after transplant, followed by a taper.

As with other prophylactic strategies, emergence of GVHD may require additional immunosuppression but does not necessitate discontinuation of ruxolitinib. Dose modifications for cytopenias and AEs are unique to this study, and generally favor supportive care to allow for

the safe continuous administration of ruxolitinib. The Protocol Officer, Protocol Chairs and protocol team members from Incyte can help guide dose modification/interruption decisions.

2.5.3.2 Tacrolimus/Mycophenolate Mofetil/Cyclophosphamide (Control)

Tacrolimus

Tacrolimus will be given per institutional practices, orally at a dose of 0.05-0.06 mg/kg/day or intravenously at a dose of 0.02-0.03 mg/kg/day starting Day +5. Starting tacrolimus dose can be modified to account for possible drug interactions (e.g., concurrent CYP3A4 inhibitor use) according to institutional guides. If starting voriconazole or posaconazole while the participant is receiving tacrolimus, it is suggested per the package insert that tacrolimus is reduced to one third of the original dose. Dose adjustments should ultimately follow institutional practices, as starting dose and dose adjustments based on blood levels also follow institutional practice. Serum levels of tacrolimus will be measured as per institutional protocols and at least weekly and dose adjusted accordingly to maintain a suggested level of 5-15 ng/mL. Tacrolimus taper can be initiated at a minimum of 90 days post HCT if there is no evidence of active GVHD. The rate of tapering will be done according to institutional practices, but participants should be off tacrolimus by Day 180 post HCT if there is no evidence of active GVHD.

Dose reductions should be made at the discretion of the provider if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Participants with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 5-10 ng/mL).

Tacrolimus may have interactions with certain foods, such as grapefruit, which should be avoided. Participants should be educated on the importance of avoiding food and beverages made with grapefruit.

Mycophenolate mofetil (MMF)

MMF will be given at a dose of 15 mg/kg/dose TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1g TID, IV or PO). MMF prophylaxis will start Day +5 and discontinue after the last dose on Day +35 or may be continued if active GVHD is present. Concurrent use of MMF with tacrolimus may increase MMF levels. Monitor for MMF-associated toxicities (see Section 2.8.4) and consider reducing the MMF dose if toxicities are thought to be related to MMF per clinical judgement.

Cyclophosphamide

Hydration prior to cyclophosphamide may be given according to institutional standards. A recommended approach is as follows: Participants are instructed to increase fluids overnight before cyclophosphamide administration. Hydration with normal saline at 3 ml/kg/hr IV will be started 2 hours prior to cyclophosphamide, then the rate will be reduced to 2 ml/kg/hr for 1 hour pre-cyclophosphamide and continued at 2 ml/kg/hr for 8 hours post-cyclophosphamide.

Mesna will be given in divided doses IV 30 minutes pre- and at 3, 6, and 8 hours post-cyclophosphamide or administered per institutional standards. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of Mesna is equal to 80%-100% of the total daily dose of cyclophosphamide.

Cyclophosphamide [50 mg/kg IBW; if ABW < IBW, use ABW] will be given on Day +3 (between 60 and 72 hours after the start of the PBSC infusion) and on Day +4 post-transplant (approximately 24 hours after Day +3 cyclophosphamide). Cyclophosphamide will be given as an IV infusion over 1-2 hours (depending on volume).

It is crucial that no systemic immunosuppressive agents, such as corticosteroids, are given from **Day 0 until 24 hours** after the completion of the post-transplant cyclophosphamide (Day +5). This rule applies only to the post-transplant cyclophosphamide arm of the study. **This includes corticosteroids as anti-emetics. However, replacement doses of chronic glucocorticoids for adrenal insufficiency are allowed.** In the matched and single mismatched setting, cytokine release syndrome (CRS) is uncommon in participants receiving PTCy. If CRS requiring intervention is encountered, tociluzumab is preferred over steroids.

2.5.4 Ruxolitinib Dosing Guidelines

2.5.4.1 Dose-Finding Run-in:

An initial dose finding run-in phase will determine the optimal dose of ruxolitinib prior to initiating the randomized Phase III portion.

Approximately 50 participants will be randomized in a 1:1 ratio in one of two dose cohorts (25 per cohort) to evaluate the safety, feasibility and efficacy of two doses of ruxolitinib when used in combination with Tac/MTX in the peri-transplant setting prior to initiating the randomized Phase III portion.

Participants will be randomized to receive ruxolitinib at one of the following doses:

Table 2.5B: Ruxolitinib Dosing Levels for Randomized Run-In Phase

Arm	Starting Dose	Concurrent Fluconazole
1	Ruxolitinib 5mg twice daily	Ruxolitinib 5mg daily
2	Ruxolitinib 10mg twice daily	Ruxolitinib 5mg twice daily

Ruxolitinib will be given in combination with Tac/MTX starting Day -1, according to the allocated arm (Table 2.5B). To be evaluable, a participant must complete at least one dose of ruxolitinib. Any participants who are not evaluable will be replaced. Participants will continue ruxolitinib treatment up to Day 364 (Cycle 14 Day 1) followed by a taper or until permanent discontinuation criteria are met (See Section 2.6)

- Subsequent dose modification for the management of adverse reactions will follow the guidelines provided in Section 2.5.4.4.
- Dose should be adjusted for concurrent use of fluconazole, as indicated in Section 2.5.4.3 (Table 2.5C).

After all run-in participants have reached Day 100, the safety, feasibility and efficacy data will be analyzed as further outlined in Chapter 5.

Once the optimal dose is determined, all subjects in the run-in cohorts between Day 101 and Day 364 of treatment are eligible to receive the optimal dose.

2.5.4.2 Randomized Phase III Portion

After the randomized run-in has determined the dose of ruxolitinib for the Phase III portion, all participants randomized to the Tac/MTX/Rux arm will start ruxolitinib on Day -1. Participants must have a creatinine clearance by Cockcroft-Gault done prior to starting dose of ruxolitinib to establish the baseline CrCl. Participants will continue ruxolitinib treatment up to Day 364 (Cycle

14 Day 1) followed by a taper or until permanent discontinuation criteria are met (See Section 2.6).

- Subsequent dose modification for the management of adverse reactions will follow the guidelines provided in Section 2.5.4.4.
- Dose should be adjusted for concurrent use of fluconazole, as indicated in Section 2.5.4.3 (Table 2.5C).

2.5.4.3 Ruxolitinib Starting Dose Adjustments for Concurrent Fluconazole and/or Renal Impairment

Fluconazole alters the metabolism of ruxolitinib and increases ruxolitinib exposure. For this reason, participants receiving fluconazole will have ruxolitinib dose reductions of 50% (one dose level). While posaconazole and voriconazole are also strong CYP3A4 inhibitors, dose adjustments are not required. Dose modifications for ruxolitinib when co-administered with other CYP3A4 inhibitors such as posaconazole, voriconazole and other antifungal therapy is not required, but participants should be monitored closely for toxicity. When fluconazole is discontinued, participants should revert to unadjusted dose of ruxolitinib.

Concomitant use of ruxolitinib with fluconazole doses of greater than 200 mg daily should be avoided.

The starting dose for each cycle will be adjusted for concurrent fluconazole according to Table 2.5C below.

Dosing should be adjusted at the beginning of each cycle related to a decrease in creatinine clearance should renal function be impaired following transplant. Etiology for renal function should be investigated and corrected where possible. Participants on hemodialysis should receive 5mg of ruxolitinib once after dialysis only on days of dialysis, if recommended by the study team to continue ruxolitinib. Dose modifications within cycles for clinically significant changes in renal function should follow the guidelines in section 2.5.4.4.

Due to the need for pharmacokinetic (PK) sampling (described in Sections 3.3.8 and 5.8.7), it is recommended that if an azole is used for fungal prophylaxis, it not be started until after the PK sample is collected. Another option if clinically indicated is to use an echinocandin (e.g. micafungin or caspofungin) for prophylaxis or control in a participant entering transplant with a controlled fungal infection.

Table 2.5C: Starting Dose Adjustments for Concurrent Fluconazole and/or Renal Impairment

CrCl ≥ 60 mL/min		**CrCl 15-59 mL/min**	
No fluconazole	With fluconazole	No fluconazole	With fluconazole
5 mg BID	5 mg QD	5 mg QD	5 mg every 48 hours
10 mg BID	5 mg BID	5 mg BID	5 mg QD

2.5.4.4 Ruxolitinib: Dose Modifications for Management of Adverse Reactions

Dose should be adjusted for adverse events as indicated in Table 2.5D. The ruxolitinib dose will be interrupted if an event outlined in table 2.5D occurs and the local principal investigator judges that AE to be possibly, probably or definitely related to the ruxolitinib. When the grade of AE requires the ruxolitinib to be modified to a lower dose, either immediately or after a hold, the ruxolitinib may be resumed at the next lower dose level, unless the local investigator deems the AE was, in retrospect, unlikely to be or not related to the ruxolitinib, at which point the original dose may be resumed. Investigators are encouraged to investigate alternative etiologies and consult with the protocol chairs prior to taking action with ruxolitinib.

The dosing levels referenced in this table are represented in Table 2.5E. Guidance is also provided for dose re-escalation in Table 2.5D. See section 2.5.4.5 on dose management for ruxolitinib to address underlying disease relapse or emerging GVHD of any grade. **Dose interruptions lasting more than 14 days requires notification to the protocol chairs.**

In general, ruxolitinib prophylaxis will be continued through grade 1-3 infections (according the BMT CTN Infection Guidelines, Appendix H). For grade 3 infections warranting a decrease in immune suppression, investigators should consult with the protocol chairs.

Table 2.5D: Dose Modifications for Ruxolitinib

Parameter	Dose Modifications
Cytopenias unrelated to malignancy, GVHD, or infection	
Platelets < 20 × 10^9/L	**Day 1-28 or until engraftment:** Monitor **Day 29 or after initial platelet engraftment-EOT**: Reduce ruxolitinib dose by 1 dose level until resolved to ≥ 20 × 10^9/L without transfusions for 7 days. If improved to > 20 × 10^9/L within 7 days, ruxolitinib dosing may return to the initial dose level. If **not** improved to > 20 × 10^9/L within 7 days, maintain ruxolitinib at 1 dose level lower.
ANC 0.50 to 0.75 × 10^9/L	**Day 1-28 or until engraftment:** Monitor; no dose modification required. **Day 29 or after engraftment - EOT**: Reduce ruxolitinib dose by 1 dose level until improved to ANC ≥ 0.75 × 10^9/L and then increase to the initial dose level. Growth factor support is allowed.
ANC < 0.50 × 10^9/L	**Day 1-28 or until engraftment:** Monitor; no dose modification required. **Day 29 or after engraftment - EOT**: Hold ruxolitinib until ANC improved to > 0.75 × 10^9/L. Resume ruxolitinib at the next lower dose level upon improvement to ≥ 0.75 × 10^9/L. May resume initial dose level when ANC > 1.0 × 10^9/L. Growth factor support is allowed.
LFT abnormalities	
Asymptomatic ALT and/or AST > 3.0 to 5.0 × ULN (Grade 2)	Maintain ruxolitinib at the same dose level.
Asymptomatic ALT and/or AST > 5.0 to 10.0 × ULN (Grade 3)	Continue ruxolitinib at 1 dose level lower until ALT and/or AST improved to Grade 2 and then, increase ruxolitinib to the initial dose level.
Asymptomatic ALT and/or AST > 10.0 to 20.0 × ULN (Grade 3)	Hold ruxolitinib until recovery to Grade 2 and then, resume ruxolitinib at 1 dose level lower.
ALT and/or AST > 20.0 × ULN (Grade 4)	Discontinue ruxolitinib.
Total bilirubin > 1.5 to 3.0 × ULN (Grade 2)	Maintain ruxolitinib at the same dose level.

Parameter	Dose Modifications
Total bilirubin > 3.0 to 5.0 × ULN (Grade 3)	Continue ruxolitinib at 1 dose level lower until recovery to Grade 1 or baseline. If recovered within 14 days, then increase by 1 dose level. If resolved in > 14 days, then maintain decreased dose level.
Total bilirubin > 5.0 to 10.0 × ULN (Grade 3)	Hold ruxolitinib until recovery to Grade 1 or baseline value. If recovered within 14 days, resume ruxolitinib at the current dose level. If resolved in > 14 days, resume ruxolitinib at one dose level lower upon recovery.
Total bilirubin > 10.0 × ULN (Grade 4)	Hold ruxolitinib until recovery to Grade 1 or baseline value. If recovered within 14 days, resume ruxolitinib at 1 dose level lower upon recovery. If not recovered within 14 days, discontinue ruxolitinib.
Concurrent ALT or AST ≥ 3.0 × ULN **and** total bilirubin ≥ 2.0 × ULN **and** ALP ≦ 2.0 × ULN	Hold ruxolitinib. Investigate for potential DILI, taking into account baseline values for LFTs, INR, and other investigations, as appropriate. Discontinue study treatment if DILI is confirmed.
Other non-hematologic, non-infectious AEs	
Grade 3	Continue ruxolitinib at 1 dose level lower until improvement to ≤ Grade 1 and then increase by 1 dose level.
Grade 4	Discontinue ruxolitinib.
In participants already receiving 5 mg every 48 hours needing further dose reduction, the dose will be interrupted until the toxicity improves back to </= grade 2. For those experiencing events while on 5 mg daily with creatinine clearance >60 and not on concurrent fluconazole the dose will also be interrupted until the toxicity improves back to </= grade 2	

Table 2.5E: Ruxolitinib Dosing Levels for Dose Modifications

Level	
1	Ruxolitinib 10mg twice daily
-1	Ruxolitinib 5mg twice daily
-2	Ruxolitinib 5mg daily

2.5.4.5 Ruxolitinib: Dosing Following Relapse or GVHD Event

If the participant experiences an underlying disease relapse as defined in section 3.2.7 or receives treatment for persistent, progressive or relapsed disease while on ruxolitinib treatment,

continuation of ruxolitinib therapy is at the discretion of the investigator. If ruxolitinib will be discontinued, the dose should be tapered rather than discontinued abruptly.

If the participant develops grade III or IV acute GVHD or chronic GVHD requiring additional immunosuppression during the ruxolitinib prophylaxis treatment period and the investigator favors continuation of ruxolitinib treatment, the participant should transition from study provided ruxolitinib to treatment with commercial ruxolitinib supply.

2.5.4.6 Ruxolitinib: Tapering

After 12 months of therapy ruxolitinib will be tapered. At Day 364, (Cycle 14, Day 1) the dose will be reduced by one dose level and dose will be tapered by one dose level every 28 days through the lowest dose level (Table 2.5F).

Reference to Ruxolitinib cycle visit information can be found in Section 2.5.3.1.

Table 2.5F: Tapering Ruxolitinib

If dose at Day 364 (end of Cycle 13) is:	Cycle 14 Day 1 reduce to:	Cycle 15 Day 1 reduce to:	Cycle 16 Day 1 reduce to:
Ruxolitinib 10mg twice daily	Ruxolitinib 5mg twice daily	Ruxolitinib 5mg daily	Ruxolitinib 5mg every 48 hours*
Ruxolitinib 5mg twice daily	Ruxolitinib 5mg daily	Ruxolitinib 5mg every 48 hours*	Off ruxolitinib
Ruxolitinib 5mg daily	Ruxolitinib 5mg every 48 hours*	Off ruxolitinib	Off ruxolitinib
Ruxolitinib 5mg every 48 hours	Off ruxolitinib	Off ruxolitinib	Off ruxolitinib

*last dose level for 14 doses/28 days

2.6 Permanent discontinuation of study treatment

2.6.1 Reason for discontinuation

Participants must be discontinued from study treatment for the following reasons:

- An unacceptable toxicity is observed. An unacceptable toxicity is defined as an AE considered related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest. This includes AEs considered related to ruxolitinib and meeting criteria for ruxolitinib discontinuation according to the guidelines provided in Section 2.5.4.4.
- Consent is withdrawn.
    - **Note**: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in the public domain, may be solicited from or collected on the participant.

Participants may choose to discontinue ruxolitinib and remain in the study for GVHD and survival follow-up.

- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The participant becomes pregnant.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, Internal Review Board (IRB), or IEC.

2.6.2 Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the End of treatment (EOT) visit should be conducted. Reasonable efforts should be made to have the participant return for the safety follow-up visit. The last date of the last dose of study treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from ruxolitinib treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the electronic Case Report Form (eCRF).
- The EOT visit should be performed, and date recorded.
- Participants must be followed for safety until the time of the follow-up visit or until ruxolitinib–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.
- Participants will continue to be followed for Patient Reported Outcomes (PRO) unless they withdraw consent for collection of follow-up data.

If the participant discontinues ruxolitinib and withdraws consent for collection of follow-up data (safety follow-up, efficacy assessments or PROs), then no additional data collection should occur; however, participants will have the option of withdrawing consent for ruxolitinib treatment but continuing in the follow-up period of the study for safety/efficacy and PRO assessments.

2.7 Supportive Care

All supportive care will be given in keeping with local institutional practice. Supportive care will be administered in a similar fashion to participants randomized to both arms of the study.

2.7.1 Growth Factors

G-CSF may be given per institutional guidelines. G-CSF may be given prior to engraftment and throughout the study period to support treatment emergent neutropenia.

2.7.2 Blood Products

Transfusion thresholds for blood product support will be consistent with standard institutional guidelines. All blood products will be irradiated.

2.7.3 Prophylaxis Against Infections

Participants will receive infection prophylaxis according to institutional guidelines. Infection prophylaxis will include, but is not limited to, agents or strategies (e.g., PCR screening and preemptive therapy) to reduce the risk of bacterial, herpes simplex, CMV, HHV-6, EBV, Pneumocystis jirovecii, and fungal infections:

- Antifungal therapy: Prophylaxis with fluconazole or other antifungal agents can be given as per local institutional guidelines. For participants on ruxolitinib, the recommended maximum dose of fluconazole daily is 200 mg.
- **Fluconazole, voriconazole and other azoles** (CYP3A4 inhibitors) are expected to increase serum tacrolimus levels, therefore, dosages of tacrolimus should be adjusted accordingly. Due to the need for pharmacokinetic (PK) sampling (described in sections 3.3.8 and 5.8.7), it is recommended that if an azole is used for fungal prophylaxis, it not be started until after the PK sample is collected. Another option if clinically indicated is to use an echinocandin (e.g., micafungin or caspofungin) for prophylaxis or control in a participant entering transplant with a controlled fungal infection.
- For participants in the Tac/MTX/Rux arm, see Table 2.5C for required dose adjustments for fluconazole.
- **CMV:** CMV monitoring will be done according to institutional guidelines. It is recommended that weekly assessment for CMV be done through Day 60 post-transplant. Use of letermovir is allowed. Any reactivation and/or CMV disease will be captured in this study. An Infection form must be submitted in Advantage eClinical.

2.7.4 Intravenous Immune Globulin

Intravenous Immune Globulin (IVIG) administration will be according to local institutional standard practice.

2.7.5 Prohibited Therapy

Hypomethylating agents and checkpoint inhibitors are prohibited from use from the time of enrollment through completion of study drug.

Planned use of donor lymphocyte infusions is prohibited.

Treatment with any other Investigational Medicinal Product (IMP) is not allowed while on study treatment. An IMP is defined as any medication without any known FDA or EMA approved indications.

Concomitant use of ruxolitinib with fluconazole doses of greater than 200 mg daily should be avoided.

Use of alternative medicine supplements is discouraged because of the possibility of interactions with the study drugs.

2.8 Participant Risks

2.8.1 Therapy Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

2.8.2 Tacrolimus

Tacrolimus side effects include:

- Cardiovascular: pericardial effusion, hypertension (which may cause arrhythmia, angina, myocardial infarction)
- Cutaneous: itching, rash
- Endocrine and metabolic: hyperglycemia, hypomagnesemia, hypokalemia, hyperkalemia, hypophosphatemia, hyperlipidemia

- Gastrointestinal: constipation, diarrhea, nausea, vomiting, anorexia, bowel perforation, dyspepsia
- General: fatigue
- Hematologic: anemia, thrombocytopenia, leukopenia, thrombotic microangiopathy
- Hepatic: liver dysfunction
- Neurologic: paresthesia, headache, tremor, encephalopathy/posterior reversible encephalopathy syndrome (PRES), dizziness, insomnia, confusion, altered mental status, seizure, blindness
- Pulmonary: pleural effusion, dyspnea
- Renal: renal impairment which may require dialysis, peripheral edema
- Miscellaneous: infection, PTLD, allergic reaction, secondary malignancy

2.8.3 Methotrexate

Methotrexate side effects include:

- Cardiac and vascular: thrombosis
- Cutaneous: photosensitivity, rash, alopecia, erythema multiforme
- Gastrointestinal: nausea, vomiting, diarrhea, pain, anorexia, ulcers, gastrointestinal bleeding, mucositis
- General: fatigue
- Hematologic: anemia, thrombocytopenia, leukopenia
- Pulmonary: pulmonary fibrosis
- Renal: nephrotoxicity
- Miscellaneous: secondary malignancy, infection

2.8.4 Mycophenolate mofetil

Mycophenolate mofetil (MMF) side effects include:

- Cardiac and vascular: hypertension, hypotension, tachycardia, edema
- Cutaneous: rash
- Endocrine and metabolic: hypocalcemia, hypokalemia, hyperuricemia, hyperkalemia, hypomagnesemia
- Gastrointestinal: nausea, vomiting, dyspepsia, abdominal pain, diarrhea
- Hematologic: leukopenia, thrombocytopenia, anemia
- Neurologic: headache, tremors, insomnia, dizziness, progressive multifocal leukoencephalopathy (PML)
- Pulmonary: dyspnea, cough, interstitial lung disease
- Miscellaneous: change in vision, infection, secondary malignancy, arthralgia, myalgia

2.8.5 Cyclophosphamide

Cyclophosphamide side effects include:

- Cardiac and vascular: heart failure (which can result in edema, effusion, dyspnea)

- Cutaneous: alopecia, rash, hyperpigmentation of skin and nails
- Gastrointestinal: nausea, vomiting, anorexia, mucositis, stomatitis, abdominal pain, diarrhea
- General: lethargy
- Hematologic: leukopenia, thrombocytopenia, anemia
- Pulmonary: pulmonary fibrosis
- Endocrine: amenorrhea, gonadal function impairment, sterility, syndrome of inappropriate antidiuretic hormone secretion (SIADH) – with associated cerebral edema
- Genitourinary: hemorrhagic cystitis
- Miscellaneous: infection, allergic reaction including anaphylaxis, secondary malignancy

2.8.6 Ruxolitinib

Ruxolitinib side effects include:

- Cardiovascular: hypertension
- Dermatologic: bruising
- Endocrine and metabolic: increased cholesterol, hypertriglyceridemia, weight gain
- Gastrointestinal: nausea, diarrhea, constipation, flatulence
- Hematologic: anemia, thrombocytopenia, neutropenia
- Hepatic: increased serum alanine aminotransferase, increased serum aspartate aminotransferase
- Musculoskeletal: muscle spasms
- Neurologic: dizziness, headache, insomnia, progressive multifocal leukoencephalopathy
- Respiratory: dyspnea
- Miscellaneous: infection (bacterial, mycobacterial, fungal or viral), non-melanoma skin cancers, allergic reaction

2.9 Study Drug Supply

Tacrolimus, methotrexate, cyclophosphamide, and mycophenolate mofetil are commercially available agents and will not be provided by the study. Refer to Section 2.5 for administration instructions.

Ruxolitinib will be provided through end of GVHD prophylaxis treatment for participants randomized to the Tac/MTX/Rux arm by Incyte. Once a participant has stopped GVHD prophylaxis with ruxolitinib or develops GVHD and receives ruxolitinib, then commercial supply must be used. Additional details regarding labeling, supply management, storage and investigational pharmacy instructions are outlined in the BMT CTN 2203 Pharmacy Manual.

CHAPTER 3

3 STUDY ENDPOINTS

3.1 Primary Endpoint

3.1.1 Randomized, dose finding portion of the trial

Multiple endpoints will be used to evaluate the objectives of the randomized, dose finding portion of the trial. Safety will be evaluated by two endpoints: graft failure by Day 28 (see definition in Section 3.2.6) and overall mortality by Day 100, for which an event is death by any cause. Feasibility will be evaluated by the proportion of participants that require a dose reduction or interruption by Day 100. Note that the following dose changes will not be counted as events in the feasibility endpoint being monitored: 1) Dose reductions defined by the protocol and intended to maintain exposure (e.g. for fluconazole interactions or for treatment emergent changes in renal function) ; 2) dose interruptions where the Ruxolitinib is held for 2 days or less; or 3) dose reductions or interruptions occurring after a disease relapse or GVHD event which is considered as a component of the GRFS endpoint definition in 3.2.1. Efficacy will be evaluated by Grade II-IV acute GVHD-free survival by Day 100. An event for this time to event outcome is defined as any of the following: 1) Grade II-IV acute GVHD, or 2) death by any cause.

Additional safety endpoints include serious adverse events (SAE) in the first 100 days, grade 2-5 AEs, and infections. All patients in the run-in study will be followed for 24 months for all study endpoints described for the randomized, phase III portion of the trial.

3.1.2 Randomized, Phase III portion of the trial

The primary endpoint for the Phase III portion of the trial is GFS up to 24 months. All randomized participants will be analyzed for this endpoint from the date of transplant. An event for this time to event outcome is defined as any of the following: 1) Grade III-IV acute GVHD, 2) chronic GVHD requiring systemic immune suppression, 3) subsequent HCT, or 4) death by any cause. The time to the event is defined as the time to the earliest of the qualifying events. Participants alive without experiencing an event will be censored at last available GVHD assessment.

The use of additional systemic immunosuppressive treatment for treatment of chronic GVHD is at the discretion of the treating physicians. For participants on the Tac/MTX/Rux arm, this refers to additional systemic treatment(s) beyond ruxolitinib. Protocol-defined escalation or modification of ruxolitinib dosing is not considered additional systemic immunosuppression for GVHD.

3.2 Secondary Endpoints

3.2.1 GVHD/relapse or Progression-free Survival (GRFS)

GVHD-free, relapse-free survival as a time to event outcome is defined as Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression, underlying disease relapse or progression, subsequent HCT, or death by any cause.

The use of systemic immunosuppressive treatment for treatment of chronic GVHD is at the discretion of the treating physicians. For participants on the Tac/MTX/Rux treatment arm, this refers to additional systemic treatment(s) beyond ruxolitinib. Protocol-defined escalation or modification of ruxolitinib dosing is not considered additional systemic immunosuppression for GVHD.

3.2.2 Chronic GVHD

The cumulative incidence of chronic GVHD will be determined. Data will be collected directly from providers and chart review as defined by the NIH Consensus Conference Criteria. Eight organs will be scored on a 0-3 scale to reflect degree of chronic GVHD involvement. Liver and pulmonary

function test results, and use of systemic therapy for treatment of chronic GVHD will also be recorded. These data will allow calculation of the NIH global severity scores of mild, moderate, and severe chronic GVHD, which has been associated with transplant related mortality and OS. Assessment of chronic GVHD will occur up to two years post-transplant.

3.2.3 Acute GVHD

Cumulative incidences of Grade II-IV aGVHD, of grade III-IV aGVHD, or of grade III-IV aGVHD or grade II aGVHD requiring second line systemic treatment will be determined. Acute GVHD will be graded according to the BMT CTN Technical Manual of Procedures (MOP) (see Appendix F). The time of onset of acute Grades II-IV and III-IV acute GVHD will be recorded, as well as the maximum grade achieved. Within the participants experiencing Grade II-IV acute GVHD, the proportion of participants with visceral involvement (liver or gut) will be described.

3.2.4 Hematologic Recovery

Hematologic recovery will be assessed according to neutrophil and platelet counts recovery after transplant. Neutrophil recovery is defined as achieving an absolute neutrophil count (ANC) greater than or equal to 500/mm^3 for three consecutive measurements on three different days. The first of the three days will be designated the day of neutrophil recovery. The competing event is death or subsequent transplant without neutrophil recovery. For participants who never drop ANC below 500/mm^3, the date of neutrophil recovery will be Day +1 post-transplant.

Platelet recovery is defined by two different metrics: the first day of a sustained platelet count greater than or equal to 20,000/mm^3 or greater than or equal to 50,000/mm^3 with no platelet transfusions in the preceding seven days. The first day of sustained platelet count above these thresholds will be designated the day of platelet engraftment. The competing event is death or subsequent transplant without platelet recovery. For participants who never drop their platelet count below 20,000/mm^3 or 50,000/mm^3, the date of platelet recovery will be Day +1 post HCT.

Lymphocyte recovery will be defined as the first day of sustained absolute lymphocyte count greater than or equal to 1000/ mm^3.

3.2.5 Donor Cell Engraftment

Donor cell engraftment will be assessed with donor/recipient chimerism studies. Chimerism may be evaluated in bone marrow or blood, as either whole marrow/blood or blood cell fractions, including CD3 and CD33 or CD15 fraction. For the purpose of this protocol, mixed chimerism is defined as the presence of donor cells, as a proportion of total cells to be less than 95% but at least 5% in the bone marrow or peripheral blood. Full donor chimerism is defined as greater than or equal to 95% of donor cells. Mixed and full chimerism will be evidence of donor cell engraftment. Donor cells of less than 5% will be considered as graft rejection. The proportion of participants with each level of chimerism described above will be described as part of this outcome. For sorted blood cell fractions, $CD3^+$ donor cell chimerism will be used to define the donor/recipient chimerism status.

3.2.6 Graft Failure

Graft failure will be assessed as secondary endpoints, including primary and secondary graft failure. Primary graft failure is defined as no neutrophil recovery to ≥ 500 cells/μL by Day 28 post HSCT. Secondary graft failure will be assessed according to neutrophil count after initial hematologic recovery. Secondary graft failure is defined as initial neutrophil engraftment followed by subsequent decline in absolute neutrophil counts < 500 cells/μL, unresponsive to growth factor therapy, but cannot be explained by disease relapse or medications. Assessment for this endpoint will occur up to two years post-transplant.

3.2.7 Disease Relapse or Progression

Relapse is defined by either morphological or molecular evidence of acute leukemia or MDS consistent with pre-transplant features. **In addition to disease specific criteria below, institution of any therapy to treat persistent, progressive or relapsed disease, including the withdrawal of immunosuppressive therapy or donor lymphocyte infusion, will be considered evidence of relapse/progression regardless of whether the criteria described above were met.**

Acute leukemia– Relapse will be diagnosed when there is:

- Reappearance of leukemia blast cells in the peripheral blood; or,
- Greater than 5% blasts in the bone marrow, not attributable to another cause (e.g., bone marrow regeneration); or,
- The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid or,
- The reappearance of cytogenetic abnormalities present prior to transplantation.

MDS – Relapse will be diagnosed when there is:

- Satisfying criteria for evolution into acute leukemia; or,
- Reappearance of MDS defining pre-transplant morphologic abnormalities, detected in bone marrow specimens; or,
- Reappearance (after prior resolution) of pre-transplant molecular or cytogenetic abnormalities in at least one metaphase on each of two separate consecutive examinations at least one month apart, regardless of the number of metaphases analyzed.

Administration of FLT3 and other tyrosine kinase inhibitors for post-transplant maintenance and for prevention of disease relapse in participant with or without minimal residual disease identified after transplant is allowed.

Lymphoproliferative Diseases – Relapse or progression will be diagnosed when there is:

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site will only be considered relapsed or progressive disease after confirmation with other modalities. In participants with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the sum of the product diameters of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by at least 50% or more and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (less than 1.5 cm in its long axis by CT).

3.2.8 Non-relapse Mortality

The cumulative incidence of NRM will be estimated at Days 100, 180, 365, and 730 after HCT. An event for this endpoint is death without evidence of disease progression or recurrence. Disease progression or recurrence will be considered competing events.

3.2.9 Toxicity and Infections

All Grade 2-5 toxicities according to CTCAE, version 5.0 will be tabulated for each intervention arm. The proportion of participants developing at least a Grade 2 or higher toxicity across intervention arms will be compared.

The incidence of definite and probable viral, fungal, and bacterial infections will be tabulated for each intervention arm. The cumulative incidence of treated CMV reactivation in the first 100 days and two years post-transplant will be described. All Grade 2 and 3 infections will be reported according to the BMT CTN Infection Grading up to Day 730 post-transplant.

3.2.10 Disease-Free Survival

Disease-free survival is the time from date of transplant to death or relapse/progression, whichever comes first. The event for this endpoint is relapse/progression or death. Participants alive and disease free will be censored at last available disease assessment.

3.2.11 Overall Survival

Overall survival is defined as the time interval between date of transplant and death from any cause. The event for this endpoint is death from any cause. Surviving participants will be censored at last follow-up.

3.2.12 Patient Reported Outcomes

Patient reported outcomes (PRO) will be measured at Baseline and then at Day 28 (1 month), Day 99 (3 month), Day 180 (6 month), Day 364 (12 month), Day 532 (18 month), and Day 730 (24 month) post-transplant using the modified Lee Chronic GVHD Symptom Scale, mMRC Dyspnea scale, Oral Health Impact Profile (OHIP-14), Ocular Surface Disease Index (OSDI), selected PROMIS subscales for gastrointestinal symptoms, physical function, cognitive function, anxiety, depression, and social function, the Work Productivity and Impairment Questionnaire (WPAI), Comprehensive Score for Financial Toxicity (COST), Patient-Reported Caregiver Assessment (PRCA) and items related to hemorrhagic cystitis symptoms, sclerotic skin symptoms, and income and insurance status. The instruments will be scored according to the recommendations of the developers. Specific PRO instruments are described in Section 4.6.4.

3.3 Exploratory Endpoints

3.3.1 Current Additional Systemic Immunosuppression-free Survival

Participants who are alive, relapse-free, and do not need additional immune suppression to control GVHD – assessed at 12 months, 18 months, and 2 years post-transplant are considered successes for this endpoint. Immune suppression is defined as any systemic agents (aside from the assigned GVHD prophylaxis regimen at randomization) used to control or suppress GVHD. Corticosteroid doses greater than 10 mg will be considered active systemic immune suppression treatment. Participants who discontinue immune suppression within 15 days or less prior to each time point of interest will be considered to be on immune suppression for this endpoint.

3.3.2 Healthcare utilization

Duration of hospital admission ("length of stay") for transplantation will be recorded in days. Number of readmissions, hospital days and days requiring escalated level of care will be captured through the full study follow-up period. Through the use of PROs, cost impact to participants will be tabulated based on data available at baseline, 12 months, 18months and 24 months post-transplant.

3.3.3 Steroid-refractory acute and chronic GVHD

Cumulative incidences of Grade II-IV and III-IV SR acute GVHD, and SR chronic GVHD will be determined. The time of onset to SR GVHD will be recorded, as well as the maximum grade or severity achieved at the time of corticosteroid failure. Organ involvement at the time of corticosteroid failure will be described. Additional lines of therapy used for SR GVHD will be captured.

Steroid-refractory GVHD will be defined as failure to achieve a complete or PR by Day 28 of systemic corticosteroids or the need to add another line of therapy.

3.3.4 Immune Reconstitution

Peripheral blood samples of T regulatory to T effector (Treg/Teff) cells, Natural Killer (NK) cells and other cellular immune subsets at Pre-Conditioning and Days 3, 14, 28, 99, 196, 364 and 730 post-HCT will be collected.

3.3.5 Vaccine Response

In centers opting into participation on the vaccine response portion, TDAP and Pneumococcal vaccines will be administered post-transplant following institutional practice. Data on TDAP and Pneumococcal titers will be collected from pre-vaccination levels and post-vaccination.

3.3.6 Organ Failure

Data on organ failure occurring through Day 100 will be collected. The incidence of definite and probable organ failure as flagged by Total Bilirubin >2 mg/dL, LVEF <30% or use of vasopressors, serum Creatinine > 2 or initiation of CRRT or intermittent hemodialysis, intubation for respiratory decompensation will be tabulated. Standard of care laboratories to tabulate EASIX (LDH, serum Creatinine, platelet count) pre-transplant, post-transplant Day 3 and Day 100 will be collected.

3.3.7 Transplant Biomarkers

A cohort of biologic samples collected prospectively from participants treated on BMT CTN 2203 will be a shared biospecimen resource for conducting future allogeneic HCT correlative studies. The sample repository and molecular and clinical databases established through the trial will be used for future analyses to facilitate studies that will establish the utility of molecular biomarkers for risk assessment, diagnosis, and monitoring. Additional analyses on participant samples using transcriptomics will answer key questions concerning: a) impact of the GVHD prophylactic regimens on biomarkers identifiable for transplant outcomes and treatment responsiveness including acute GVHD, chronic GVHD, non-relapse mortality, or organ failure as identifiable through urine and/or serum specimens.

3.3.8 Pharmacokinetic

Pharmacokinetic (PK) assessment for ruxolitinib will include the following PK parameters: C_{max}, t_{max}, C_{min} and $AUC_{(0\text{-}t)}$. A central laboratory will perform all laboratory assessments for PK. Timing for blood PK collection is presented in Table 3.3A and Table 3.3B. Details and methods for obtaining, processing, handling, and shipping of blood samples will be provided in the Laboratory

Manual for this study. The exact date and time of PK blood draws will be recorded in the eCRF along with the date and time of ruxolitinib administration.

PK samples will be collected as follows:

- 50 participants from the run-in collecting PK at four timepoints on Cycle 1, on Day +2, +3 or +4 post HCT (day of sampling may vary to avoid falling on a weekend day), and one additional PK sample at predose on a day in Cycle 1 on Day 21 (± 7 days) post HCT (see Table 3.3A).
- 150 participants in the Phase III Ruxolitinib arm collecting PK at two timepoints on Cycle 1, on Day +2, +3 or +4 post HCT (day of sampling may vary to avoid falling on a weekend day), and one additional PK sample at predose on a day in Cycle 1 on Day 21 (± 7 days) post HCT (see Table 3.3B).

Table 3.3A: Pharmacokinetic Sample Collection Time for Ruxolitinib for Dose-Finding Run-in

Study Visit	Timing of Samples
Cycle 1 Day +2, +3, or +4 post HCT	Predose (within 90 minutes of receiving ruxolitinib) 1 hour post dose (± 15 min) 2 hours post dose (± 30 min) 1 sample between 4 and 6 hours post dose
Cycle 1 Day 21 (± 7 days) post HCT	Predose (within 90 minutes of receiving ruxolitinib)

Table 3.3B: Pharmacokinetic Sample Collection Time for Ruxolitinib for Phase III

Study Visit	Timing of Samples
Cycle 1 Day +2, +3, or +4 post HCT	Predose (within 90 minutes of receiving ruxolitinib) 1 hour post dose (± 15 min)
Cycle 1 Day 21 (± 7 days) post HCT	Predose (within 90 minutes of receiving ruxolitinib)

3.4 Endpoint Review Process

Upon completion of any participant follow-up, an Endpoint Review Committee (ERC) will conduct an independent review of site-reported data on key study endpoints to determine the endpoint data to be presented in the primary manuscript and final analysis. This Committee will consist of members of the protocol team, including the Protocol Chairs, Protocol Officer, Operational Statistician, and Protocol Coordinator. Each participant's data will be reviewed by ERC clinicians. The adjudicated endpoint data for each participant will be determined by consensus of their reviewers.

The ERC will employ a risk-based strategy to the data review. First, a random sample of 20% of the total study population will be chosen. The key endpoints will be determined in two ways: using

ERC adjudications and using the site-reported data. The concordance between the ERC adjudicated and site-reported endpoints will be computed. If the concordance is 90% or above, the ERC will end, and site-reported endpoints will be used for all statistical analyses. If the concordance falls below 90%, a second random subset of 20% of study participants will be drawn from the unadjudicated participants. Then, the concordance between ERC adjudicated and site-reported endpoints in the combined first and second subsets will be computed. If the concordance is 90% or above, the ERC will end, and site-reported data will be used for all statistical analyses. Otherwise, all remaining, unadjudicated participants will undergo review and the ERC adjudicated endpoints for the entire study population will be used in all statistical analyses.

Data will be obtained from the relevant case report forms and source documents and will be provided to reviewers in a blinded manner with respect to treatment assignment, treatment center, and participant identifier. These data will be kept confidential and will not be discussed outside the Committee or presented in a public forum.

CHAPTER 4

4 PARTICIPANT ENROLLMENT AND EVALUATION

4.1 Approaching Participants, Eligibility Screening, and Obtaining Consent

Participants will be approached for this study after the decision to proceed with transplantation is made and an HLA-matched PBSC donor is identified. Participants willing to participate in the trial will sign an NMDP IRB-approved consent form. Transplant physicians will evaluate the participant eligibility for randomization onto this study (see Section 2.4). Transplant center personnel will record the documentation of participant consent and register the participant in Advantage eClinical (an Electronic Data Capture (EDC), system). Participants will also need to sign the CIBMTR "Protocol for a Research Database for Hematopoietic Cell Transplantation and Marrow Toxic Injuries" consent form since future laboratory correlative studies using any remaining stored research samples require linking with clinical data collected by CIBMTR.

4.2 Transplant Protocol Registration

Following consent, participants are to be screened into the Interactive Response Technology (IRT) system to receive an assigned study ID. The participant must also be enrolled into the screening segment in Advantage eClinical system. Following enrollment into screening, eligibility criteria will be verified. Ineligible participants will not be randomized, and no further follow-up will be obtained beyond screen failure reason. Before randomization occurs for eligible participants, the transplant center must state through Advantage eClinical which conditioning regimen and which maintenance regimen (if any- see inclusion criteria) will be used for the enrolled participant. Such a registration step will avoid potential biases that preferential use of a certain regimen on one treatment arm could confer to the study.

4.3 Randomization

Once the participants has given written informed consent, and the transplant center has confirmed participant eligibility and registered the participant's conditioning and maintenance regimen (see inclusion criteria), confirmation of eligibility is entered into the Advantage eClinical EDC system. Once eligibility is confirmed in the EDC system, randomization then occurs in the IRT system with same day confirmation of randomization in the Advantage eClinical data management system. Participants should not be randomized more than 14 days prior to the planned initiation of conditioning. If initiation of conditioning has not started within 14 days of randomization, the Protocol Coordinator and Protocol Chairs and Officer must be notified.

Participants randomized to the ruxolitinib arm of the study will continue to be followed in the IRT system for the purpose of study drug management. Participants randomized to the post-transplant cyclophosphamide arm of the study will not require any additional management in the IRT system after randomization.

4.4 Treatment Scheduling

Treatment should be initiated as soon as possible after randomization. This will prevent participant attrition prior to transplant for reasons such as disease progression. Consequently, all treatments related to the transplant should be scheduled **prior** to randomization. This includes planning an admission date and ensuring that the PBSC donor can be mobilized and undergo apheresis in a coordinated fashion with the planned transplant.

4.5 Participant Evaluation

The participant pre-transplant evaluation must be completed within 60 days of randomization (exceptions noted in the Study Calendar Table 4.6B. See Section 4.6.2 Pre-transplant Evaluations for more information). This step is necessary because participant organ function, infection status, and status of malignancy may vary over time. This evaluation will protect participants with a new contraindication to transplant from initiating transplant therapy at an unsafe time.

4.6 Study Monitoring

The follow-up schedule for scheduled clinical study visits is outlined in Table 4.6A. Participants on both arms are required to follow the same schedule, except where noted for ruxolitinib tapering. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User's Guide.

Table 4.6A: Clinical Follow-Up Schedule

Study Visit	Target Day Post-Transplant
Day of Transplant	Day 0*
Day 3	Day 3 - 1 day¥
1 week	7 ± 3 days
2 weeks	14 ± 3 days
3 weeks	21 ± 3 days
4 weeks (Cycle 2, Day 1)	28 ± 3 days
5 weeks	35 ± 3 days
6 weeks	42 ± 3 days
7 weeks	49 ± 3 days
8 weeks (Cycle 3, Day 1)	56 ± 3 days
9 weeks	63 ± 3 days
10 weeks	70 ± 3 days
11 weeks	77 ± 3 days
12 weeks (Cycle 4, Day 1)	84 ± 3 days
14 weeks (Day 100 visit)	99 ± 7 days
16 weeks (Cycle 5, Day 1~)	112 ± 7 days
Day 180 visit/ Cycle 8, Day 1~	196 ± 7 days
Cycle 11, Day 1~)	280 ± 7 days

Study Visit	Target Day Post-Transplant
12 months post-transplant/ Cycle 14, Day 1^	364 ± 7 days
Cycle 15, Day 1+	392 ± 7 days
Cycle 16, Day 1+	420 ± 7 days
18 months post- transplant	532 ± 28 days
24 months post-transplant	730 ±60 days

*If infusion occurs over 2 days, the day of transplant should be recorded as the day the first infusion occurred.

¥ Day 3 to be completed on Day 2 or Day 3 and prior to start of PTCy for participants on the PTCy arm.

^For participants on the ruxolitinib arm, the ruxolitinib taper is recommended to begin at the start of Cycle 14.

+Optional visits for ruxolitinib arm participants, depending on ongoing ruxolitinib taper.

~A three cycle supply of Ruxolitinib will be dispensed at this visit for participants on the Tac/MTX/Rux arm.

4.6.1 Participant Assessments

Table 4.6B summarizes participant clinical assessments over the course of the study.

Table 4.6B: Participant Clinical Assessments[1]

	Screen-ing	Pre-condi-tioning[15]	Pre-infusion	0	3	7	14	21	28	35	42	49	56	63	70	77	84	99	112	196 (6 mo post-txp)	280	364[13] (1 yr post-txp)	392/420[13]	532 (18 mo post-txp)	730 (2 yr post-txp)	EOT[11]
History, physical exam, weight and height[2]	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	
Karnofsky performance status (see Appendix D)	X																	X				X			X	
HCT-Specific Comorbidity Index score	X																									
Disease Risk Index (see Appendix E)	X																									
Donor and recipient HLA typing[12]	X																									
CBC[3], differential, platelet count, and blood chemistries[4]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	
Lipid Panel	X												X					X				X		X		
Infectious disease titers[5]	X																									
EKG	X					X		X																		
LVEF	X																									
DLCOcorr and FEV1predicted	X																									
Disease evaluation[6]	X																	X				X		X	X	
Chest x-ray or chest CT	X																									
Pregnancy test[7]	X								X				X				X		X	X	X	X	X			X
GVHD assessments[8]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity assessments[9]				X					X				X					X	X	X	X	X	X			X
Infection assessments	X			X			X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
Chimerism[10]	X								X									X								
Patient Reported Outcomes	X								X									X		X		X		X	X	
Blood for future research		X	X			X	X	X	X				X					X		X	X	X			X	
Pharmacokinetic[14]					X			X																		
Vaccine Response																				X	X					
Immune Reconstitution (peripheral blood)		X			X		X		X									X		X		X			X	
Urine for future research		X	X			X	X	X	X				X					X		X						

Table 4.6B Footnotes:

[1] Refer to Table 4.6A for visit windows.

[2] Height is only required at baseline. It is not required to be repeated at the other time points.

[3] CBC with differential performed three times weekly from Day 0 until ANC at least 500/mcL or greater for three days and platelet count at least 20,000/mcL or greater after nadir, while hospitalized. CBC then performed weekly through Day 84 post-transplant, then at Days 99, 196, 280 364, 532 and 730 post-transplant.

[4] Blood chemistries include: serum creatinine, albumin, bilirubin, alkaline phosphatase, AST and ALT. Blood chemistries performed twice weekly until hospital discharge. Blood chemistries performed weekly after hospital discharge until Day 84 post-transplant, then at Days 99, 196, 280, 364, 532 and 730 post-transplant. Standard of care laboratories to tabulate EASIX (LDH, Serum Creatinine, platelet count) to be collected labs to be collected pre-transplant, post-transplant Day 3 and Day 99.

[5] Infectious disease titers should be performed per institutional guidelines and may include: CMV, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.

[6] Evaluation of disease: (A) For acute leukemia, CML, and MDS, evaluation for malignant disease includes a bone marrow aspirate and biopsy for pathology and cytogenetics. **A bone marrow biopsy must be performed no more than 44 days prior to the initiation of conditioning.** (B) For lymphomas, bone marrow biopsy and/or imaging studies are appropriate for disease evaluation and will be done according to institutional practices. Participants with lymphomas should undergo the same post-transplant testing as their pre-transplant evaluation for matter of subsequent comparison. **Imaging studies must be done no more than 60 days prior to participant randomization.**

[7] Female participants of childbearing potential require a serum pregnancy test at screening, EOT, and the safety follow-up visits. A serum or urine pregnancy test will be performed at screening, on Day -1 prior to the first dose of ruxolitinib and on Day 1 of every treatment cycle. A positive urine pregnancy test requires immediate interruption of study drug until a serum pregnancy test is performed. If the serum pregnancy test result is negative after a urine test result was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study treatment and continue participation in the study. If a pregnancy is confirmed by a serum pregnancy test result, see Section 4.7.4 for reporting requirements.

[8] GVHD assessments performed weekly from Day 7 until Day 84 post-transplant, and then at Days 99, 112, 196, 280, 364, 392, 420 532 and 730. The GVHD assessment will include a review of **all** abnormalities experienced **during the entire assessment period** and the **highest grade** for each abnormality during the assessment period will be recorded on the Acute GVHD form and the Follow-up/Chronic GVHD form in eClinical. The Chronic GVHD Provider Survey will record GVHD symptoms present in the last week (*whether attributed to GVHD or not*) and must be completed by a clinician on the day of the assessment.

[9] The toxicity assessment will include a review of **all grade 2 and higher** toxicities experienced **during the entire assessment period** and the **highest grade** for each toxicity during the assessment period will be recorded on the Toxicity form in eClinical. Once a participant has met an event for the primary endpoint (Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression or subsequent HCT), toxicity assessment must be completed at the next scheduled visit through the date the primary endpoint event occurred. Additional toxicity assessments are not required beyond having an event for the primary endpoint for participants on the PTCy arm. Participants randomized to Rux are required to completed an End of Treatment safety visit. For participants on the ruxolitinib arm that develop chronic GVHD, immune suppression is defined in sections 2.5.4.5 and 2.9 if continuing with ruxolitinib treatment.

[10] Chimerism may be evaluated in bone marrow, whole blood or blood cell fractions, including CD3 and CD33 or CD15 fraction, according to institutional practice. The actual measurement dates may be within +/- 7 days of the recommended time points. The screening chimerism test noted refers to the collection of pre-transplant donor and recipient samples for post-transplant chimerism studies.

[11] End of Treatment safety visit not required for participants in cyclophosphamide/tacrolimus/MMF arm. **The End of Treatment visit should occur at least 30 days after the last dose of ruxolitinib.**

[12] If recipient has a 7/8 unrelated donor, DSA testing will be performed.

[13] A final safety assessment for any outstanding adverse events should be performed at the first visit occurring at least 30 days after the last dose of ruxolitinib. This assessment should be performed at the Day 364 visit for participants not receiving ruxolitinib. After the final safety assessment, BMT CTN reporting standards to report unanticipated serious adverse events should continue through completion of study follow-up.

[14] Pharmacokinetic (PK) at the first time point has a +/- 1 day window and can be collected at Day +2, +3, or +4; PK at the second time point has a +/- 7 day window and can be collected between Day +14 and Day +28.

[15]Visits only required for phase 3 portion of the study. Not required for dose finding run-in.

4.6.2 Pre-transplant Evaluations

The following observations must be completed within 60 days prior to participant randomization, or 74 days prior to initiation of conditioning regimen unless otherwise indicated.

- History, physical examination, height, and weight.
- Karnofsky performance status.
- HCT-Specific Comorbidity Index score must be done prior to start of conditioning
- CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, and lipid panel.
    - A CBC with differential and platelet count must be collected at pre-conditioning and pre-infusion where a future research PBMC is obtained.
    - A creatinine clearance using Cockcroft-Gault should be established pre-conditioning for dosing considerations of ruxolitinib.
- Infectious disease titers should be performed per institutional guidelines and may include: CMV antibody, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus (HSV), syphilis, HIV and HTLV I/II antibody, and varicella zoster.
- EKG and LVEF – **can be performed within 90 days prior to participant randomization.**
- Pulmonary function tests, including DLCO and FEV1 - **can be performed within 90 days prior to participant randomization.**
- HLA typing of participant and donor. HLA typing can be performed at any time prior to randomization.
    - Sibling donors must be HLA typed for HLA-A and -B at intermediate (or higher) resolution, and -DRB1 at high resolution using DNA-based typing.
    - Unrelated donors must be HLA typed for HLA-A, -B, -C and -DRB1 at high resolution using DNA-based typing.
- Disease evaluation for participants with acute leukemia, CML or MDS includes a bone marrow aspirate and biopsy for pathology and cytogenetics. A bone marrow biopsy must be performed no more than 44 days prior to the initiation of conditioning.
- Disease evaluation for participants with lymphomas includes imaging studies for matters of comparison post-transplant, the types of which may be determined according to the center's institutional practices. Imaging studies must be done no more than 60 days prior to participant randomization.
- Chest X-ray or chest CT.
- Female participants of childbearing potential require a serum or urine pregnancy test at screening. A serum or urine pregnancy test will be performed at screening, on Day -1 prior to the first dose of ruxolitinib.
- PROs to be completed by English or Spanish speaking study participants, prior to randomization.
- Pre-transplant donor and recipient samples for post-transplant chimerism studies.
- Blood sample collection for immune reconstitution.
- Donor Specific Antibodies (DSA) if using a 7/8 URD

- Optional blood sample collection for future biomarker analysis.
    - Pre-conditioning samples to be collected between Day -14 and Day -7
    - Pre-infusion samples to be collected between Day -1 and Day 0
- Optional urine collection for future research.
- Data on occurrence of Grade II and III infections and recorded as per the BMT CTN Technical MOP.

4.6.3 Post-transplant Evaluations

The following observations will be made according to Table 4.6B:

- History and physical exam to assess GVHD and other morbidity. GVHD will be monitored in accordance with BMT CTN guidelines as specified in the BMT CTN Technical MOP (BMT CTN MOP). GVHD assessments weekly from Day +7 through Day +84 post-transplant, and then as per Table 4.6B.
- Assessment for toxicities as per Table 4.6B
    - Once a participant has met an event for the primary endpoint (Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression or subsequent HCT), toxicity assessment must be completed at the next scheduled visit through the date the primary endpoint event occurred. Additional toxicity assessments are not required beyond having an event for the primary endpoint for participants on the PTCy arm. Participants randomized to Rux are required to completed an End of Treatment safety visit. For participants on the ruxolitinib arm that develop chronic GVHD, immune suppression is defined in sections 2.5.4.5 and 2.9 if continuing with ruxolitinib treatment.
- CBC with differential performed at least three times a week from Day 0 until ANC at least 500/μL for 3 consecutive measurements over 3 days and platelet count at least 20,000/μL for 3 days without platelet transfusion in the prior 7 days (while hospitalized only) after nadir is reached. Thereafter, CBC weekly until Day 84 post-transplant, then as per Table 4.6B.
    - A CBC with differential and platelet count must be collected at timepoints where a future research PBMC is obtained.
- Serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST, twice a week until hospital discharge and then weekly until Day 84 post-transplant, then as per Table 4.6B.
- Electrocardiogram (ECG) monitoring at Days 7, 21.
- Female participants of childbearing potential require a serum or urine pregnancy test on Day 1 of every treatment cycle. A positive urine pregnancy test requires immediate interruption of study drug until a serum pregnancy test is performed. If the serum pregnancy test result is negative after a urine test result was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study treatment and continue participation in the study. If a pregnancy is confirmed by a serum pregnancy test result, see Section 4.7.4 for reporting requirements.
- Chimerism studies performed at Days 21 and 99 post-transplant. Chimerism may be evaluated in bone marrow, whole unfractionated blood, or blood cell fractions, including CD3 and CD33 or CD15 fraction. The actual measurement dates may be within +/- 7 days of the recommended time points (see Appendix B).

- Disease evaluation of the malignant disease at Days 99, 364, 532, and 730 post-transplant: For acute leukemia, CML and MDS this includes a bone marrow aspirate and biopsy for pathology and cytogenetics. For lymphomas this includes imaging studies, which will be done according to institutional practices and the same as prior to transplant, for matter of comparison.
- Data on occurrence of Grade II and III infections and recorded as per the BMT CTN Technical MOP.
- PROs to be completed by English or Spanish speaking study participants at Days 28, 99, 196, 364, 532 and 730.
- Blood sample collection for immune reconstitution. Note: The Day 3 sample can be collected on either Day 2 or Day 3, but must be prior to the start of PTCy for participants randomized to the PTCy arm.
- Optional blood sample collection for future biomarker analysis.
- Optional urine collection for future research.
- Pharmacokinetic (PK) collection at Cycle 1, on Day +2, +3, or +4 post-transplant (day of sampling may vary to avoid falling on a weekend); PK collection at Day 21± 7 days

4.6.4 Patient Reported Outcomes

The CIBMTR Survey Research Group (SRG) centrally coordinates all Patient Reported Outcome (PRO) survey assessments. At the time a participant is enrolled into Advantage eClinical, the SRG receives an email notification and adds that participant to CIBMTR's electronic Patient Reported Outcomes (ePRO) system for data collection tracking. Transplant Centers provide participant contact information securely to the SRG.

Baseline PRO surveys will be collected by the center electronically or on paper forms after consent and before randomization. Day 28 PRO surveys will also be collected by the center. Centers will be provided with paper PDFs of the survey and a set of unique electronic survey links in both English and Spanish for each time point. Surveys may also be administered verbally if needed. Centers will record participant responses on a paper copy of the survey contemporaneously while reading survey questions and response choices to the participant. Electronically collected PRO surveys are directly entered in the ePRO system via the unique links. Centers will scan and securely email baseline and Day 28 PRO surveys recorded on paper to the SRG, who will enter the data into the ePRO system.

The SRG will centrally collect all post-treatment PRO surveys starting at Day 99 (3 Months). Centers will securely provide participant contact information to the SRG before the 3 Month window opens. At Day 99 (3 Months), the SRG will attempt to contact the participant by phone to confirm contact information, remind them of survey assessment time points and confirm how they want to complete PRO surveys (paper or electronic). After speaking by phone with the participant, or if they are unreachable by phone, the SRG will send the Day 99 survey assessment by email and/or mail. The SRG will continue to contact the participant via email, phone and/or mail to collect survey assessments at required study timepoints. The SRG will follow-up by phone and e-mail with non-responders up to approximately six contact attempts or until the visit window closes, to minimize missing surveys. If the SRG is unable to get response from enrolled participants, they may request that local study coordinators remind participants or administer the PRO surveys at clinical visits. The SRG may also administer surveys verbally by phone if needed. The SRG will record participant responses in the electronic version of the survey contemporaneously while reading questions and response choices to the patient.

PRO surveys will be available in English and Spanish languages. Participants who are unable to complete PRO surveys in English and Spanish are still eligible for the study and will complete all non-PRO assessments.

4.6.4.1 Patient Reported Outcomes Measurement Information System (PROMIS) Domains

Nine PROMIS domains will be used to measure detailed functioning and symptom burden for participants (Appendix G). PROMIS measures utilize T-score metrics, with higher scores indicating more of the concept (i.e., physical function or depression). Scores are normalized to 50 with a standard deviation of 10, and scores greater than 0.5 times standard deviation (i.e., <45 or >55, compared to the general population) are considered clinically meaningful.

The PROMIS domains are GI-Nausea and vomiting, GI-Diarrhea, GI-Disruptive swallowing, Fatigue, Physical function, Cognitive function, Anxiety, Depression, Satisfaction with Participation in Social Roles. Additionally, two global quality of life and health status items will be included.

4.6.4.2 Modified Lee Chronic GVHD Symptom Scale

The modified Lee chronic GVHD symptom scale (mLSS) is a 28-item measure with seven domains referent to the past seven days: skin, mouth, eye, lung, psychoemotional, vitality and nutrition.[30] Responses are captured on a five-point Likert scale ("no symptoms, or not bothered at all," "slightly bothered," "moderately bothered," "bothered quite a bit," or "extremely bothered"). Scores for each domain are converted to a 0-100 scale in which higher scores indicate more bother. The mLSS has distinguished between people with different severities of chronic GVHD and been used in randomized clinical trials to show difference in treatment arms.[31, 32] Although participants will not have chronic GVHD before transplant, the instrument will still be administered at baseline to capture any pre-existing symptoms and aid in interpreting post-transplant scores.

4.6.4.3 Individual Symptom Scales

To measure symptom burden related to chronic and acute GVHD, PRO assessments related to dyspnea, hemorrhagic cystitis, sclerotic skin, oral impacts and ocular impacts will be used.

The Modified Medical Research Council (mMRC) Dyspnea scale assesses the degree of functional disability due to dyspnea.

Two items from the BMT CTN 1703 PRO surveys are used to measure hemorrhagic cystitis symptom burden.

The Oral Health Impact Profile (OHIP) measures dysfunction, discomfort and disability caused by oral conditions.[33, 34]

The Ocular Surface Disease Index (OSDI) measures symptoms and vision effects of dry eye disease.[35, 36]

4.6.4.4 Financial impact scales

The Work Productivity and Impairment Questionnaire (WPAI), Comprehensive Score for Financial Toxicity (COST), Patient-Reported Economic, Income and Insurance Data (PREIID) and items about income and insurance measure the impacts of treatment on finances and economic status of the patient households.[37]

The Patient Reported Caregiver Assessment (PRCA) measures the type of support provided by caregivers, and the economic burden to patient caregivers.

4.6.4.5 PRO Compensation

To compensate participants for their effort and time and ensure high compliance on PRO surveys, gift cards will be distributed to study participants for PRO survey completion. Participants will

receive one gift card for each completed PRO survey timepoint. Each pre-paid visa gift card will be valued at $20 and will be mailed to the address provided by the participant. The SRG will track all completed surveys, distribute gift cards to recipients and manage gift card inventory.

4.6.4.6 PRO Schedule of Assessments

The selection of PRO assessments varies by time point based on when symptoms or changes in status are expected. The table below shows the schedule of individual PRO assessment and the overall survey length at each time point.

Table 4.6C: PRO Schedule of Assessments

	Items (Minutes)	Baseline (pre-random)	Day 28 (1m) +/- 3	Day 99 (3m) +/- 14	Day 180 (6m) +/- 14	Day 364 (12m) +/-28	Day 532 (18m) +/- 28	Day 730 (24m) +/-28
1 PROMIS Global items	2 (<1)	X	X	X	X	X	X	X
2 mMRC Dyspnea scale	1 (<1)	X	X	X	X	X	X	X
3 Hemorrhagic Cystitis items	2 (<1)	X	X	X				
4 OHIP-14	14 (2-3)						X	
5 OSDI	12 (2-3)						X	
6 PROMIS GI – Nausea and Vomiting	3 (1)	X	X	X		X	X	X
7 PROMIS GI – Diarrhea	2 (<1)	X	X	X		X	X	X
8 PROMIS GI – Disruptive Swallowing	4 (1)	X	X	X	X	X	X	
9 PROMIS Fatigue	44 (1)	X	X	X	X	X		
10 PROMIS Physical Function	8 (1-2)	X	X	X	X	X		
11 PROMIS Cognitive Function	4 (1)	X		X	X		X	
12 PROMIS Anxiety	4 (1)	X		X			X	
13 PROMIS Depression	4 (1)	X		X			X	
14 PROMIS Social Function	4 (1)	X		X	X	X	X	X
15 Modified Lee cGVHD Symptom Scale	28 (2)	X		X	X	X	X	X

	Items (Minutes)	Baseline (pre-random)	Day 28 (1m) +/- 3	Day 99 (3m) +/- 14	Day 180 (6m) +/- 14	Day 364 (12m) +/-28	Day 532 (18m) +/- 28	Day 730 (24m) +/-28
16 Income/ Insurance	6 (1-2	X				X	X	X
17 WPAI	6 (1-2)	X				X	X	
18 PREIID								X
19 COST	12 (2-3)	X				X	X	X
20 PRCA	2-6 (1-2)	X		X		X	X	X
Total		104 (18-20)	26 (5-6)	86 (15-14)	61 (9-8)	102 (18-20)	104 (17-20)	93 (14-15)

4.6.5 Data Reporting in Advantage eClinical

Criteria for timeliness of submission for all study forms are detailed in the eCRF Completion Guide and User's Guide. Forms that are not entered into Advantage eClinical within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the Advantage eClinical and integrated into the eClinical master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

4.6.5.1 Reporting Participant Deaths

Recipient death information must be entered into Advantage eClinical within 24 business hours of knowledge of the participant's death. If the cause of death is unknown at that time, the eCRF can be submitted without this information. Once the cause of death is determined, the form must be updated in Advantage eClinical.

4.7 Adverse Event Reporting

4.7.1 Definitions

Adverse Event: An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms.
- Requires active intervention.
- Requires interruption or discontinuation of study drug.
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

Serious Adverse Event: A serious adverse event (SAE), as defined in 21 CFR 312.32, is any AE that results in one of the following outcomes, regardless of causality and expectedness:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expected reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above (e.g., suspected transmission of an infectious agent by a medicinal product is considered an SAE). Any event is considered an SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Anticipation:

- **Anticipated adverse events** are those that are listed in the protocol, the informed consent document, or have been previously identified as resulting from the underlying disease or the transplant process.
- **Unanticipated adverse events** would include those that have not been listed in the protocol, the informed consent document, or have not been previously identified as resulting from the underlying disease or the transplant process. Unanticipated events also include events that would normally be anticipated, but vary in nature, intensity, or frequency, as determined by the investigator.

Expectedness:

- **Expected adverse events** are those that have been previously identified as resulting from administration of the study drug. For the purposes of this study, an adverse event is considered expected when it appears in the Investigator's Brochure as a known safety risk.
- **Unexpected adverse events** are those that are not listed as a known risk in the Investigator's Brochure or vary in nature, intensity, or frequency from those known risks.

4.7.2 Classification of Adverse Events by Severity

The severity refers to the intensity of the reported event. The Investigator must categorize the severity of each reportable SAE according to the NCI CTCAE Version 5.0. CTCAE guidelines can be referenced at the following website: http://ctep.cancer.gov/reporting/ctc.html. For any term that is not specifically listed in the CTCAE scale, intensity will be assigned a grade of one through five using the following CTCAE guidelines:

- **Grade 1**: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
- **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care activities of daily living
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death related to AE

4.7.3 Classification of Adverse Events by Relationship to Investigational Product

The relationship of each reported event to the study treatment will be assessed by the Investigator; after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the SAE, temporal relationship to any study treatment interventions and de-challenge or re-challenge according to the following guidelines:

- **Possibly, Probably, or Definitely Related:** there is a reasonable possibility that the study treatment caused the event. A relationship of possibly, probably, or definitely related to the investigational product is considered related for the purposes of regulatory authority reporting.
- **Unlikely, or Not Related:** There is no reasonable possibility that the investigational product caused the event. An unlikely or not related relationship to the investigational product is not considered related for the purposes of regulatory authority reporting.

4.7.4 Required Adverse Event Reporting

Adverse event reporting will be consistent with BMT CTN procedures (BMT CTN Administrative MOP, Chapter 6). It is BMT CTN policy that AEs must be reported even if the investigator is unsure whether a relationship exists between the AE and the use of the study treatment ruxolitinib. AEs will be reported in Advantage eClinical using NCI's CTCAE Version 5.0.

AE Reporting Period

The AE reporting period for this trial starts once the participant has signed informed consent and ends with the end of treatment safety visit, which should occur at least 30 days after the last dose of ruxolitinib. Investigators are not obligated to actively seek SAE information after this reporting period. Any unanticipated serious adverse events are still required to be reported through completion of all study follow-up, per BMT CTN standards.

Anticipated/Expected Event Collection

Many anticipated and expected AEs will be collected at regular intervals as defined on the Form Submission Schedule, including calendar-driven case report forms (e.g., Toxicity and GVHD) or event-driven case report forms (e.g., Relapse/Progression, Infection, and Death). The toxicity form will collect many anticipated and expected grade 2-5 events through the study follow-up

period. These events are listing in Appendix I of the protocol. Infection and GVHD events will be collected on their respective forms and will not need to be entered separately on an AE form unless they meet serious criteria AND are related to the study drug. If an anticipated event collected on the toxicity form meets SAE criteria and occurs during the AE reporting period, it will need to be entered as an SAE through the AE reporting form set as well. If an event is reported on the toxicity form and is assessed as being at least possibly related to the study drug ruxolitinib, it should be separately reported on an AE form.

Non-Serious AE Reporting

Any non-serious CTCAE grade 2-4 event that occurs during the AE reporting period and that is not collected on another form (e.g., toxicity, GVHD, relapse, infection, death) must be reported through the AE reporting system via Advantage eClinical. For these non-serious events, a simplified Adverse Event Form will collect basic information.

Serious AE Reporting

All reportable SAEs that occur during the AE reporting period, regardless of expectedness/anticipation, will be entered through an expedited AE reporting system via Advantage eClinical **within 24 hours of knowledge of the event.** As mentioned earlier, events of GVHD and infection are only reported as SAEs if they meet serious criteria AND are related to study drug. After the AE reporting period, only unanticipated SAEs, life-threatening events not collected on another form, or events assessed as at least possibly related to study product will be collected in this system.

If there are network outages, a paper copy of the AE forms must be completed and emailed to 2203Safety@emmes.com to initiate Sponsor review. Once the system is available, the event information must be entered into the system. Prompt reporting of SAEs by the investigator in eClinical is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study drug/treatment under clinical investigation are met.

After the initial expedited SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Follow-up information for each reportable SAE is also recorded in the eCRF and transmitted to the Sponsor's pharmacovigilance system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug because of the SAE (e.g., dose reduced, interrupted, or discontinued), or participant disposition (e.g., continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event.

If the SAE is also a suspected unexpected serious adverse reaction (SUSAR), the Sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. Anticipated events that are listed in Appendix I of this protocol will not be reported individually to the FDA as SUSARs, regardless of relationship assessment per section VI.A of the FDA guidance entitled "Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies". SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Investigator safety letters (ISLs) must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary. The Sponsor or its designee may issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SUSAR has been reported. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary

or listing of SAEs) from the Sponsor (or designee) will review and then file it along with the IB and will notify the local IRB/IEC, if appropriate, according to local requirements.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

The Data and Safety Monitoring Board (DSMB) will receive reports of all SUSARs upon review by the BMT CTN Medical Monitor. Summary reports of all reported SAEs will be reviewed by the DSMB on an annual basis.

Form guidance based on type of event and timeline:

Table 4.7C: AE Reporting Form Guidance

Type of Event	AE Reporting Period	After AE Reporting Period through Study Follow-Up
Death	AE form Death form	Death form AE form if related or unanticipated
Grade 2-5 Anticipated Event captured on the Toxicity form*	Toxicity form	Toxicity form
Grade 2-5 Anticipated Event captured on the Toxicity form that meets SAE criteria*	Toxicity form AE form	Toxicity form AE form if also related – see next row
Grade 2-5 Anticipated Event captured on the Toxicity form that is related to study drug*	Toxicity form AE form	Toxicity form AE form
Grade 2-4 AE not collected on another form (all Grade 5 events will be collected on a Death form) *	AE form	AE form if grade 4 AE form if also unanticipated –see next row
Unanticipated SAE	AE form	AE form
Event related to study drug	AE form	AE form
Infection	Infection form	Infection form
Infection meeting SAE criteria and related to study drug	Infection form AE form	AE form
GVHD	GVHD form	GVHD form
GVHD meeting SAE criteria and related to study drug	GVHD form AE form	AE form

* Once a participant has met an event for the primary endpoint (Grade III-IV acute GVHD, chronic GVHD requiring systemic immune suppression or subsequent HCT), toxicity assessment must be completed at the next scheduled visit through the date the primary endpoint event occurred. Additional toxicity assessments are not required beyond having an event for the primary endpoint for participants on the PTCy arm. Participants randomized to Rux are required to completed an End of Treatment safety visit. For participants on the ruxolitinib arm that develop chronic GVHD, immune suppression is defined in sections 2.5.4.5 and 2.9 if continuing with ruxolitinib treatment.

4.7.5 Potential Drug-Induced Liver Injury

In the event a participant has

1. an increase in ALT or AST elevation ≥ 3 × ULN, and
2. a total bilirubin ≥ 2 × ULN, and
3. an ALP < 2 × ULN,

clinical tests (e.g., blood, including prothrombin time/INR, and imaging tests) must be performed frequently as per standard of care until resolution and/or stabilization. In addition, a diagnostic workup must be performed to exclude alternative causes, such as viral hepatitis, liver GVHD, or administration of other drug(s) known to be hepatotoxic or confirmed Hy's law.

If a potential drug-induced liver injury (DILI) is also classified as an SAE, the SAE and follow-up reporting requirements in Section 4.7.4 should be followed. Of particular note, if the workup does not identify an alternative cause for the liver injury, the Investigator should review the important medical event SAE classification, as the Sponsor considers these events that have no other apparent etiology to be important medical events and requests expedited reporting.

4.7.6 Procedure in Case of Pregnancy

If a female participant becomes pregnant during the study dosing period or within 30 days from the last dose of study drug, the investigator should report the information through an expedited AE reporting system via Advantage eClinical. If a partner of a male participant becomes pregnant during the study dosing period or within 90 days from the last dose of study drug, the investigator should report the information through an expedited AE reporting system via Advantage eClinical. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, neonatal data and other related information will be requested. If a participant becomes pregnant during the study dosing period, the IMP will be discontinued.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) are mentioned below.

- “Spontaneous abortion” includes miscarriage, abortion, and missed abortion.
- Death of an infant within 30 days after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 30 days after birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as “possible” by the investigator.
- In the case of a delivery of a living newborn, the “normality” of the infant is evaluated at the birth.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

Information will be collected at the time of delivery/birth and 180 and 360 days after birth.

4.8 CIBMTR Data Reporting

Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR).

Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment in BMT CTN 2203 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post- transplant Comprehensive Report Forms must also be submitted for all participants enrolled on this trial. CIBMTR forms will be submitted directly to CIBMTR at the times specified on the Form Submission Schedule.

CHAPTER 5

5 STATISTICAL CONSIDERATIONS

5.1 Study Design

The study is designed as a Phase III randomized, open label, multicenter trial to compare investigational Tac/MTX/Rux versus PTCy/Tac/MMF for GVHD prophylaxis in participants with controlled malignant disease receiving an allogeneic PBSC transplant after a RIC regimen. The primary endpoint is GFS as a time to event endpoint, with up to two years of follow up on all participants. There will also be a randomized run-in study of 50 participants to evaluate two doses of ruxolitinib when used in combination with Tac/MTX and select the dose that will be used in the randomized Phase III portion of the trial. The target enrollment is 572 participants total, including 50 on the run-in study, and 522 participants on the randomized Phase III trial (261 participants on each of the two treatment arms).

5.1.1 Accrual

It is estimated that 48 months of accrual will be necessary to enroll the targeted sample size with an accrual rate of approximately 14 participants per month. Both Core and Affiliate Centers will enroll participants on this study. Accrual will be reported by race, ethnicity, gender, and age.

5.1.2 Randomization

All participants will be randomized within 14 days prior to the initiation of conditioning therapy. Randomization will be performed in a 1:1 ratio using random block sizes for the two arms during both the safety run-in and the main phase III portion of the study. Randomization will be stratified only during the phase III portion of the trial by donor match [7/8 or matched (8/8 or 6/6)] and by disease risk using Disease Risk Index (DRI Low, Intermediate and High). The DRI level “High” will include participants classified as both “High” and “Very High”.

5.1.3 Primary Endpoint

The primary endpoint is GFS as a time to event endpoint from the time of transplant. Events for GFS are detailed in Section 3.1. All participants are scheduled to be followed for the primary endpoint for two years; however, the primary endpoint will be analyzed as a time to event endpoint.

5.1.4 Primary Hypothesis

There are two co-primary hypotheses for non-inferiority and superiority of the Tac/MTX/Rux arm compared to PTCy/Tac/MMF on the primary endpoint of GFS. These hypotheses will be tested in sequence with non-inferiority testing conducted first, and if the non-inferiority hypothesis is rejected, we will proceed to test for superiority. For superiority testing, the null hypothesis is that the HR between Tac/MTX/Rux vs. PTCy/Tac/MMF for the GFS endpoint is equal to one vs. an alternative that it is less than 1, i.e.,H_{0s}: HR = 1 vs. H_{as}: HR < 1. This null hypothesis will be tested using a one-sided 2.5% significance level, if the non-inferiority test is rejected first. The non-inferiority null hypothesis is based on a fixed margin approach. To determine the non-inferiority margin, note that BMT CTN 1703 demonstrated that the active control in the current trial, PTCy/Tac/MMF, has a HR of 0.60 (95% CI 0.45-0.80) compared to Tac/MTX without ruxolitinib. Using the upper 95% confidence limit (HR = 0.80) and trying to preserve 50% of the effect on the log HR scale, leads to a non-inferiority margin on the HR scale of 1.12. Therefore, the non-inferiority null hypothesis is H_{0n}: HR ≥ 1.12 vs. H_{an}: HR < 1.12. Note that if we consider these NI hypotheses on the 18-month GFS probability scale instead of the HR scale, the null and alternative hypotheses can be approximately interpreted as follows, assuming GFS of approximately 55% at 18 months based on CIBMTR and BMT CTN 1703 data: the null hypothesis

is that the 18-month GFS for Tac/MTX/Rux is 4% or more worse in absolute probability than that for PTCy/Tac/MMF, against the alternative that it is not 4% or more worse.

5.2 Sample Size and Power Considerations

Power calculations for both the non-inferiority and superiority objectives are described here for several true hazard ratios. The primary superiority analysis will be done using a stratified log-rank test at a one-sided significance level of 2.5%, with the randomization factors used as stratification variables. The primary non-inferiority analysis will be done using a stratified Cox model, with the randomization factors used as stratification variables; if the upper bound for the 95% confidence interval for the HR is < 1.12 then we will reject the non-inferiority null hypothesis. We assume the PTCy/Tac/MMF arm has a piecewise linear survival curve with GFS of 63% at 12 months and 55% at 18 months, based on data from BMT CTN 1703 as well as CIBMTR data on similarly treated participants. We also assume there is 5% exponential rate of loss to follow-up by 18 months, and that the treatment arm has proportional hazards. Although the protocol will include follow-up to 2 years to include follow-up after discontinuation of ruxolitinib, we ignore this for the purposes of a conservative power calculation since CIBMTR data indicates that relatively few events occur after 18 months. We will target a total of 201 events which will provide 85% power for the superiority objective to detect a true HR of 0.65 (corresponding approximately to a 13% absolute improvement in GFS at 18 months) as well as 85% power for the non-inferiority objective when the true HR is 0.73 (corresponding approximately to a 10% absolute true improvement in GFS at 18 mo). Note that this is a more conservative effect size than what preliminary data in Table 1.3 suggests (81% vs. 62% GFS at 1 year, for a HR of 0.44). Enrollment of n = 522 participants with 18 months follow-up on all participants is expected to meet the event and power requirements, based on the GFS and loss to follow-up distribution assumptions above. Power calculations for other true HRs for non-inferiority and superiority with 201 events are shown in Table 5.2A below.

Table 5.2A: Power Calculations for Non-inferiority and Superiority

True HR (absolute 18- month GFS difference)	Power for Superiority	Power for Non-inferiority
1.00 (0%)	NA	12%
0.73 (10%)	59%	85%
0.65 (13%)	85%	97%

5.3 Interim Analysis and Stopping Guidelines

5.3.1 Randomized Run-In Phase

An initial randomized run-in phase will evaluate the safety and efficacy of two doses of ruxolitinib when used in combination with Tac/MTX in the peri-transplant setting prior to initiating the randomized Phase III portion. The run-in will employ a randomized, open-label, parallel-cohort design to determine the tradeoffs between the dose levels and select a dose of ruxolitinib for the randomized phase III study. The run-in will randomize 25 participants to one of two dosing cohorts (Table 2.5B). After enrollment of 50 participants (25 to each dose cohort) and confirmation of receipt of dosing, enrollment will be closed until the starting dose for the Phase III population is defined.

Key safety endpoints are graft failure by Day 28 and overall mortality by Day 100, the key feasibility endpoint is proportion of participants requiring dose reduction or interruption, and the

key efficacy endpoint is a short-term measure of activity: Grade II-IV acute GVHD-free survival by Day 100 (events defined as Grade II-IV acute GVHD or death by day 100). Sequential monitoring of each of these 4 endpoints will be conducted continuously. If any stopping boundaries are crossed, the DSMB will be notified so that they can review the safety data. If this review leads to closure of one of the study doses, the other dose will continue as a nonrandomized single arm study. If the review leads to closure of both doses, no further doses will be considered at this time and the study will end. Doses will be considered acceptable for further consideration if they do not cross any of the stopping boundaries by the end of the run-in enrollment plus 100 day follow up period after the last enrolled participant. If both doses are considered acceptable, further comparisons between the doses will be conducted to identify a dose for further study in the randomized Phase III study.

Note that this run-in study will not have formal statistical comparisons of these arms, as it is not powered for this purpose. Rather a descriptive analysis only will be conducted and will look for clinically relevant observed differences of 10% or more between dose levels to guide dosing decisions. If differences in all key endpoints are not observed the optimal starting dose of ruxolitinib in combination with tac/MTX will be defined as 5mg BID. Table 5.3A below shows the likelihood of observing a 10% or more difference in outcomes, both when there is no difference and when there is a 20% true difference between dose arms. Likelihood of observing >=10% difference in safety endpoints is small (5%-11%) when there is no difference between dose arms, and is high (81-85%) when there is a 20% difference in arms. Analysis of the run-in study will be reviewed by the protocol team in order to select the dose level for the Phase III trial, based on the totality of the safety, feasibility, efficacy and PK data. In addition to the day 100 analysis for dose selection, patients on the run-in study will continue to be followed through 24 months for other study endpoints as detailed in the phase III trial endpoints section, and these outcomes will be described once follow-up is complete. Data from the run-in study will not be incorporated into the Phase III trial analysis. Analysis details for the run-in study will be detailed in a separate Statistical Analysis Plan, but briefly, all randomized participants who proceed to transplant and receive at least one dose of Ruxolitinib will be included in the analysis population. Participants will be analyzed in the dose level group to which they are randomized. Estimates of binary outcomes will be summarized using frequencies and percents, while survival or competing risks endpoints subject to censoring will be estimated using the Kaplan-Meier method and the Aalen-Johansen estimator respectively. 95% confidence intervals will be provided using exact methods for binary outcomes and the complementary log-log transformation for survival or cumulative incidence estimates. Missing data will not be imputed due to limited sample sizes, and participants that withdraw or are lost to follow up will be assumed to be censored at random. No formal comparisons will be made between randomized starting dose levels due to limited sample size.

Table 5.3A: Probability of observing >=10% higher rate in higher dose arm compared to lower dose arm for each key endpoint of interest in run-in study with n=25 per group

		Probability of seeing >=10% higher rate in higher dose arm	
	Assumed rate for lower dose	**When Delta=0%**	**When Delta=20%**
Primary graft failure by Day 28	5%	5.0%	85.0%
Overall mortality by Day 100	10%	11.5%	82.1%
Rate of dose reductions/interruptions by Day 100	20%	18.9%	78.6%
Grade 2-4 Acute GVHD free survival at Day 100	60%	23.8%	79.0%

Sequential Monitoring of Run-in Study

The run-in study will continuously monitor the rates of each of these 4 events separately in each dose arm using a sequential boundary, and if the boundary is crossed, the Data and Safety Monitoring Board (DSMB) will be notified for further review of the dose safety. Boundaries are constructed using maximum acceptable rates (null rates) of 5% for graft failure within 28 days, 10% for mortality within 100 days, 20% for dose interruption/reduction within 100 days, and 40% for Grade 2-4 acute GVHD or death within 100 days. All boundaries are constructed using a truncated Sequential Probability Ratio Test (SPRT) with a 10% type I error rate and a target alternative rate which is 15% higher than the null rate. Stopping rules are implemented using the 'stoppingrule' R package. Stopping rules for each endpoint are shown in Table 5.3B below as a function of the number of participants evaluable. Operating characteristics are shown in Table 5.3C below.

If the stopping boundary is crossed for the feasibility endpoint (dose reductions + dose interruptions), the totality of the data will be reviewed. This review will look to better characterize the feasibility of the doses used in the run-in. Information that will be accounted for in this evaluation could include (but are not limited to): number of dose reductions versus dose interruptions, duration of interruptions (with dose holds > 14 days being considered significant interruptions), the percentage of intended doses received (calculated from initiation of ruxolitinib until first GRFS event), and whether the interruption event was considered related to ruxolitinib. Note that the following dose changes will not be counted as events in the feasibility endpoint being monitored: 1) Dose reductions defined by the protocol and intended to maintain exposure (e.g. for fluconazole interactions or for treatment emergent changes in renal function) ; 2) dose interruptions where the Ruxolitinib is held for 2 days or less; or 3) dose reductions or interruptions occurring after a disease relapse or GVHD event which is considered as a component of the GRFS endpoint definition. Even if both dosing arms (5 mg BID and 10 mg BID) trigger the

feasibility stopping rule, the protocol team and DSMB may still recommend that the study proceed to the phase 3 randomized portion of the trial.

Table 5.3B: Sequential Boundaries for DSMB Review in Run-in, applied separately by study arm.

	Stopping boundary: stop if # of events is >=x			
# of participants evaluable	**Graft failure by Day 28**	**Overall mortality by Day 100**	**Dose interruptions / reductions by Day 100**	**Grade 2 to 4 acute GVHD or death by Day 100**
3	2	3	3	-
4	2	3	4	-
5	2	3	4	5
6	2	3	4	6
7	2	3	5	6
8	2	3	5	7
9	3	4	5	7
10	3	4	5	8
11	3	4	6	8
12	3	4	6	9
13	3	4	6	9
14	3	4	6	10
15	3	4	7	10
16	3	5	7	11
17	3	5	7	11
18	3	5	7	12
19	4	5	8	12
20	4	5	8	13
21	4	5	8	13
22	4	6	9	14
23	4	6	9	14

	Stopping boundary: stop if # of events is >=x			
# of participants evaluable	**Graft failure by Day 28**	**Overall mortality by Day 100**	**Dose interruptions / reductions by Day 100**	**Grade 2 to 4 acute GVHD or death by Day 100**
24	**4**	**6**	**9**	**14**
25	**4**	**6**	**9**	**15**

Table 5.3C: Stopping probabilities of Sequential Boundaries during Run-in, as a function of the delta values for the event rate.

Delta**	Graft Failure	Mortality	Dose interruptions / reductions	Grade 2 to 4 Acute GVHD or Death
0%	**10%**	**10%**	**10%**	**10%**
10%	**64%**	**52%**	**42%**	**35%**
15%	**83%**	**73%**	**62%**	**53%**
20%	**93%**	**87%**	**79%**	**71%**

**** Increase over null value of 5% for GF, 10% for mortality, 20% for dose interruptions/reductions, and 40% for grade 2 to 4 acute GVHD or death**

5.3.2 Interim Analysis for Efficacy in the Phase III Trial

One interim analysis for efficacy and non-inferiority will be conducted at approximately 75% information fraction. The stopping boundary will be constructed using a Lan-DeMets error spending approach with O'Brien-Fleming approximation error spending function. This boundary would have critical value of 2.3397 and significance level 0.0096 at the first interim analysis (75% information, or 151 events), and critical value 2.0118 and significance level 0.0221 at the final interim analysis (100% information, or 201 events). The same boundary will be applied to both non-inferiority and superiority monitoring, using a group sequential closed test procedure, with overall stopping of the study only if superiority is shown.[38] The probability of stopping for efficacy at the first interim analysis when the true HR is 0.65 is 61.5%, while the overall power by the end of the study will be 85.4%. The targeted number of events for the interim analysis is anticipated to occur at approximately 42 months out of a planned 45 months of accrual. While it will have minimal impact on halting accrual of participants, it could allow for substantially earlier dissemination of study results.

5.3.3 Guidelines for Safety Monitoring

Monitoring of four key safety endpoints (overall mortality by 100 days post-HCT, primary graft failure by Day 28 post-HCT, SUSARs by day 28, and grade 3-4 acute GVHD by day 100 in the subgroup of patients transplanted using a 7/8 unrelated donor) will be conducted separately in each treatment arm, and if any rate significantly exceeds pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN MOP. The monitoring guidelines serve as a trigger for consultation

with the DSMB for additional review and are not formal “stopping rules” that would mandate automatic closure of study enrollment. Toxicity, AEs, and other safety endpoints will be monitored regularly and reported to the DSMB annually at a minimum; in the event that any safety concerns arise, these data will be conveyed to the DSMB expeditiously.

Monitoring rule for overall mortality by 100 days post-HCT:

The rate of mortality will be monitored up to Day 100 post-HCT separately in each of the two treatment arms. The expected probability of Day 100 mortality after a RIC transplant is 10%, based on BMT CTN 1703 data. The null hypothesis that the Day 100 mortality rate is less than or equal to 15% is tested separately in each treatment arm using an extension of the sequential probability ratio test (SPRT) for censored exponential data— See Appendix C for more details on SPRT.

This SPRT is based on testing the null hypothesis that the 100-day mortality rate is less than or equal to 10%. The sequential testing procedure conserves type I error at 5% across all of the assessments and can be represented graphically. At each interim analysis, the total time on study (e.g., in months or years, x axis) is plotted against the total number of endpoints (e.g., participants experiencing death, y axis). The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring to protect against excessive 100-day mortality. If the number of events crosses above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment reaches the target maximum of 261 participants per arm. This procedure assumes an exponential distribution for the time until death during the first 100 days and censors follow-up time at Day 100. Only deaths that occur on or before the participant has been followed for 100 days are counted. Total time on study is computed as time from transplant to death or to Day 100, whichever comes first, summed for all participants on study. A SPRT contrasting 10% versus 20% Day 100 mortality rate results in decision boundaries with a common slope of 0.0477 and an upper intercept of 3.3113 with nominal type I and II errors of 7.5 % and 10%, respectively. Because of truncation of the SPRT at a finite sample size the actual type I and II errors will usually be lower than nominal levels.

The actual operating characteristics of the truncated test were determined in a simulation study that assumed uniform accrual of 261 participants over a 45-month period, exponential time to failure after HCT, and implemented monthly monitoring of the SPRT. In practical implementation, however, the SPRT is monitored monthly and also reviewed each time a new event occurs to identify any crossing of a toxicity boundary in between monthly assessments. The actual error rates are shown in Table 5.3D.

Table 5.3D: Operating Characteristics of the Sequential Probability Ratio Test for Day 100 Mortality with 100,000 Simulation Replicates

True Day 100 Mortality Rate	10%	15%	20%
Probability Reject Null	0.049	0.601	0.983
Mean Month Stopped	47	31	13
Mean Number of Day 100 Mortality Events	25	25	14
Mean Number of Participants Enrolled	252	170	77

For example, the testing procedure rejects the null hypothesis in favor of the alternative 4.9% of the time when the true Day 100 mortality rate is 10%, and 98.3% of the time when the rate is 25%. This corresponds to a type I error rate of α = 0.049 and a type II error rate of β = 0.017. When the true Day 100 mortality rate is 20%, on average, the DSMB will be consulted 13 months after opening, when 14 events have been observed in 77 participants.

Monitoring rule for graft failure by 28 days post-HCT

Graft failure is expected to be no higher than 5% by 28 days. Graft failure within 28 days will be monitored using a SPRT for binary data that compares a rate of 5% under the null hypothesis to a rate of 15% under the alternative hypothesis. This sequential testing procedure preserves the type I error rate at a prespecified level across all of the monthly examinations. The binary SPRT can be represented graphically by plotting the number of evaluable participants against the cumulative number of events. The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring in order to protect against excessive Day 28 graft failure rates. If the cumulative number of graft failures falls above the upper boundary the SPRT rejects the null hypothesis and concludes that more graft failures occurred than should be expected in the observed number of evaluable participants. Otherwise, the SPRT continues until enrollment reaches the target sample size of 261 participants.

This procedure considers only graft failures occurring by Day 28. A binary SPRT contrasting 5% versus 15% Day 28 graft failure rates results in decision boundaries with a common slope of 0.0919 and an upper intercept of 2.1722 with nominal type I and II error rates of 6.5% and 10%, respectively. Because the SPRT employed here is truncated at a sample size of 261 and only uses the upper decision boundary, the actual type I and II errors will vary from these nominal levels.

The actual operating characteristics of the truncated test are shown in Table 5.3E, obtained from a simulation study that assumed uniform accrual of 261 participants over a 45-month period. This simulation study implemented monitoring of the SPRT after each additional participant became evaluable. In practical implementation, however, the SPRT is monitored monthly and also reviewed each time a new event occurs to identify any crossing of a toxicity boundary in between monthly assessments.

Table 5.3E: Operating Characteristics of the Binary SPRT for Day 28 Graft Failure from a Simulation Study with 10,000 Replicates

True Day 28 Graft Failure Rate	5%	10%	15%
Probability Reject Null	0.052	0.738	0.998
Mean Month Stopped	44	23	8
Mean # events by Day 28	13	13	6
Mean # Participants Enrolled	250	128	43

The testing procedure rejects the null hypothesis in favor of the alternative 5.0% of the time when the true Day 28 graft failure rate is 5% and 99.8% of the time when the rate is 15%. This corresponds to a type I error rate of 5.0% and a type II error rate of 0.2%. If the true Day 28 graft

failure rate is 15%, the DSMB will be consulted 8 months after opening on average, when 6 events have been observed in 43 participants.

Monitoring rule for SUSARs by 28 days post-HCT

Serious, Unexpected and Suspected Adverse Reactions (SUSAR) are expected to be no higher than 5% by 28 days, based on data from BMTCTN 1703. SUSARs within 28 days will be monitored using a SPRT for binary data that compares a rate of 5% under the null hypothesis to a rate of 15% under the alternative hypothesis. This monitoring rule and its operating characteristics are identical to the rule for graft failure; refer to that section above for further details.

Monitoring rule for cumulative incidence of grade 3-4 acute GVHD by Day 100 in subgroup of participants transplanted using a 7/8 unrelated donor

The incidence of grade 3-4 acute GVHD occurring by Day 100 post transplant will be monitored separately in each arm in the subset of patients transplanted using an unrelated donor matched at 7/8 to the patient. This subset is expected to be <=15% of the overall population, or approximately 40 patients per arm. Death in the absence of grade 3-4 acute GVHD is treated as a competing risk for this event. The Day 100 incidence of grade 3-4 acute GVHD is not expected to exceed 10%. A safety monitoring boundary for grade 3-4 acute GVHD was developed using a TITE-SPRT[39] that contrasts a 10% null rate to a 30% targeted excessive rate. The nominal type I error rate for this procedure is 5%, corresponding to a critical value of 12.256 for the probability ratio and a rejection boundary with intercept 1.856 and slope 0.186 for the number of events versus effective sample size.

At each examination, the effective sample size (ESS) is computed, defined as the total number of patients whose Day 100 acute GVHD status is known plus the total days follow up in patients with pending day 100 acute GVHD status divided by 28 days. The ESS counts each patient whose status is known (either because an acute GVHD event or death was observed before Day 100 or they completed 100 days of follow up without acute GVHD or death) as a full subject, whereas a patient who is event-free and has not reached 100 days is counted as a fractional subject. The ESS can be viewed as the total exposure of trial patients to the investigational therapy and can equivalently be described as the total person-days of evaluation among transplanted patients, which equals 100 x ESS days. Table 5.3F displays the pausing guideline for grade 3-4 aGVHD. The ESS is compared to the rejection boundary value for the number of grade 3-4 acute GVHD events within 100 days. At least 3 events must be observed in order to trigger review.

Table 5.3F: Monitoring Guideline for grade 3-4 aGVHD by Day 100 in subgroup of participants transplanted using a 7/8 unrelated donor

Effective Sample Size	Total Person-days Evaluated	Rejection Boundary for # grade 3-4 aGVHD Events
3.00 – 6.143	300 – 614	3
6.144 – 11.514	614 – 1151	4
11.515 – 16.886	1152 – 1689	5
16.887 – 22.257	1689 – 2226	6

Effective Sample Size	Total Person-days Evaluated	Rejection Boundary for # grade 3-4 aGVHD Events
22.258 – 27.629	2226 – 2763	7
27.630 – 33.000	2763 – 3300	8
33.001 – 38.371	3300 – 3837	9
38.372 – 40.000	3837 – 4000	10

Table 5.3G shows the operating characteristics of this test over a range of true grade 3-4 acute GVHD incidence rates. Uniform accrual of 40 mismatched unrelated donor transplant recipients over a 45 month period is assumed. The operating characteristics were computed using 100,000 Monte Carlo simulations under the assumption that grade 3-4 acute GVHD events are uniformly distributed over the first 100 days post transplant. This procedure rejects the null hypothesis 4.7% of the time when the true grade 3-4 acute GVHD rate by day 100 is 10% and 89.9% of the time when the rate is 30%. If the true rate is 30%, the monitoring rule will be triggered and the DSMB will be consulted at approximately 21 months after opening on average, when 5 events have been observed in 18 enrolled participants.

Table 5.3G: Operating Characteristics of Sequential Monitoring Procedure for grade 3-4 acute GVHD by day 100 in a subgroup of participants transplanted with a 7/8 unrelated donor

True incidence of grade 3-4 aGVHD by day 100	10%	15%	20%	25%	30%
Probability of Early Pausing	0.047	0.207	0.474	0.734	0.899
Mean Month Stopped	46.8	42.5	35.4	27.5	20.8
Mean # Events	3.9	5.3	5.9	5.8	5.2
Mean # Participants Enrolled	38.9	35.6	30.1	24.0	18.5

* Operating characteristics were estimated using 100,000 Monte Carlo simulations per scenario.

5.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all participants. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, disease-specific risk categories, DRI, hematopoietic cell transplant comorbidity index (HCT-CI), donor type and HLA matching, donor/recipient CMV status, donor/recipient sex match, donor/recipient ABO match, conditioning regimen, and planned post-transplant maintenance therapy.

5.5 Analysis Populations

5.5.1 Run-in Analysis Population

All participants who proceed to transplant and receive at least one dose of Ruxolitinib wil be included in the analysis population for the run-in study. Participants will be analyzed in the dose level group to which they are assigned.

5.5.2 Primary Efficacy Analysis Population

An intention-to-treat (ITT) population will serve as the population for the primary analysis of efficacy, for the co-primary superiority and non-inferiority endpoints, as well as for key secondary endpoints. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

5.5.3 Transplant Population

A modified intention-to-treat (mITT) population will serve as the population for the analysis of secondary post transplant endpoints for the randomized phase III study. All randomized participants who proceed to transplant will be included in this population; based on BMT CTN 1703, we expect that only a small percentage of participants (< 3%) will not go on to a transplant, and these participants will be described separately. Participants will be analyzed in the treatment group to which they are randomized.

5.5.4 Safety Population

The safety analysis population in this study will comprise all participants “as treated” in the study. This population will be used for the analysis of safety data. The “as treated” safety population consists of all randomized participants who received a HCT with one of the two randomized GVHD prophylaxis regimens. Participants will be included in the treatment group corresponding to the study treatment (GVHD prophylaxis) they actually received for the analysis of safety data using the “as treated” population. For most participants this will be the treatment group to which they are assigned.

5.6 Analysis of Primary Endpoint

A Statistical Analysis Plan (SAP) containing all the analysis details will be finalized prior to database lock. All analyses will be conducted according to the SAP unless otherwise noted. The primary endpoint of the trial is GFS from the time of transplant, treated as a time to event variable. Participants going off study drug without prior documentation of a GFS event will continue to be followed for GFS, and this additional follow-up will be included in the primary analysis. Participants without a GFS event who are lost to follow-up will be censored at GVHD assessment. The primary analysis will be conducted when 201 events have been observed for the primary endpoint, or when the last participant has reached 2 years of follow up, whichever occurs first. Analysis of GFS will be conducted by first testing for non-inferiority, and if significant, we will proceed to testing for superiority. Non-inferiority analysis will be conducted using the Primary Efficacy Analysis Population; the HR for GFS with the Tac/MTX/Rux arm versus the PTCy/Tac/MMF arm, along with ninety-five percent confidence intervals, will be estimated from a stratified Cox model with treatment as a covariate, with strata based on the variables used to stratify the randomization. To assess non-inferiority, the upper bound of the 95% CI for the HR will be compared to the non-inferiority margin of 1.12; if it is below the margin, we will conclude non-inferiority. The primary efficacy analysis will consist of a comparison of GFS in the Primary Efficacy Analysis Population by treatment arm based on a stratified log-rank test, with the same strata based on the variables used to stratify the randomization. A significance level of 0.025 (one-sided) will be used to test the null hypothesis of no difference between the treatments. The estimate for the treatment effect

will be the hazard ratio and 95% confidence interval in the Primary Efficacy Analysis Population. This will be estimated from a stratified Cox model with treatment as a covariate, and using the same strata variables. Kaplan-Meier curves will be constructed to estimate GFS probabilities for each treatment group, and 95% CIs will be provided at 18 months and 24 months. Sensitivity analyses may be conducted looking at different censoring rules. For example, 1) censor participants who miss multiple consecutive GVHD assessments prior to missing these multiple assessments, and 2) censor participants who go off treatment without documentation of a qualifying GVHD event for the primary endpoint. Finally, the proportional hazards assumption for the Cox model will be assessed using graphical methods and time-dependent covariates, and if there is evidence that this assumption is violated, adjusted GFS curves will be generated, and adjusted GFS probabilities will be compared between the groups at 18 months and 24 months. We also will conduct subgroup analyses of the primary endpoint by sex, race, ethnicity, age, disease, conditioning regimen, comorbidity index, and donor type/HLA matching.

5.7 Analysis of Secondary Endpoints

Secondary endpoints will be formally tested, in sequence, in order to control the Familywise Error Rate. Endpoints will only be considered significant if all preceding tests in the sequence are also significant. Otherwise, analyses after a non-significant result in the sequence will be considered exploratory. The sequence of testing of secondary endpoints, after non-inferiority and superiority for the primary endpoint have been established as 1) GRFS, 2) Chronic GVHD requiring Immune Suppression, 3) Grade III-IV acute GVHD or Grade II aGVHD requiring second line systemic treatment, 4) DFS, and 5) OS.

5.7.1 GRFS

Kaplan-Meier curves will be constructed to estimate GRFS probabilities for each treatment group using the Primary Analysis Population, and 95% confidence intervals will be provided at 18 months and 24 months. The HR, along with ninety-five percent confidence intervals, will be estimated from a stratified Cox model with treatment as a covariate, with strata based on the variables used to stratify the randomization.

5.7.2 Chronic GVHD

Incidence of chronic GVHD requiring additional systemic immunosuppression will be estimated using the cumulative incidence function, treating death and second transplant prior to chronic GVHD as competing risks. Estimates and confidence intervals will be provided at 18 months and 24 months. Cumulative incidence of chronic GVHD will be compared between treatment arms using a Fine and Gray model, adjusting for strata variables used in randomization. Results will be summarized using the subdistribution HR and its associated 95% confidence interval. Supportive analyses of the cumulative incidence of all chronic GVHD, and of moderate-to-severe chronic GVHD will be conducted in a similar manner. In addition, distribution of maximum grade of chronic GVHD will be tabulated in each arm.

5.7.3 Acute GVHD

Incidence of acute GVHD Grade III-IV or Grade II requiring second line systemic treatment will be estimated with 95% confidence intervals for each treatment group at Days 100, 180 and 364 (1 year), using the cumulative incidence estimate, treating death and second transplant prior to aGVHD as competing events. Cumulative incidence of acute GVHD will be compared between treatment arms using a Fine and Gray model, adjusting for strata variables used in randomization. Results will be summarized using the subdistribution HR and its associated 95% CI. Maximum acute GVHD grade and visceral involvement will be described in each arm using frequencies. A supportive analysis of all grade II-IV aGVHD and of Grade III-IV aGVHD will also be conducted in a similar way.

5.7.4 Hematologic recovery

Probabilities of neutrophil recovery by Day 28 and Day 100 will be described with 95% CIs for each treatment group using the cumulative incidence estimate, treating death or second transplant as competing events. Similarly, probabilities of platelet recovery by Day 60 and Day 100 and lymphocyte recovery by Day 60 and Day 100 will be described with 95% CIs for each treatment group using the cumulative incidence estimate, treating death and second transplant as a competing event. These cumulative incidence curves will be compared using Gray's test. Primary and secondary graft failures will be described using frequencies.

5.7.5 Donor cell engraftment

Donor chimerism at each collection time point after transplantation in each of the randomized treatment arms will be described numerically as median and range for those evaluable as well as according to proportions with full (> 95% donor cell), mixed (5.0-94.9% donor cells), graft rejection (< 5%), or death or second transplant prior to assessment of donor chimerism. Comparisons between quantitative donor chimerism at each time point will be done using Wilcoxon rank sum test, while comparisons between categorical donor chimerism groups will be done using chi-square tests.

5.7.6 Disease Relapse or Progression

Incidence of disease relapse or progression at two years will be estimated with 95% CIs for each treatment group using the cumulative incidence estimate, treating death prior to disease relapse as a competing event. Cumulative incidence of disease relapse or progression will be compared between treatment arms using a Fine and Gray model, adjusting for strata variables used in randomization. Results will be summarized using the subdistribution HR and its associated 95% CI.

5.7.7 Non-relapse Mortality

Incidence of non-relapse mortality (NRM) at Days 100, 180, 364 (1 year), and 730 (2 years) will be estimated for each treatment group using the cumulative incidence estimate, treating disease relapse or progression as a competing event. Cumulative incidence of NRM will be compared between treatment arms using a Fine and Gray model, adjusting for strata variables used in randomization. Results will be summarized using the subdistribution HR and its associated 95% CI.

5.7.8 Toxicity and Infections

All Grade 2-5 toxicities according to CTCAE version 5.0 will be categorized by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and the number of AEs will be summarized by SOC, preferred term, and peak grade. The number and percentage of participants with at least one Grade 2 or higher toxicity will be summarized by SOC and the preferred term. Detailed listings of unexpected SAEs, including severity and relationship to treatment, will be presented. Toxicities and unexpected SAEs will be summarized using the safety population.

The number of infections and the number of participants experiencing infections will be tabulated by type of infection, severity, and time period after transplant. The cumulative incidence of CMV reactivations requiring treatment will be described at Day 100 and Day 730 (2 years) with a 95% CI, treating death as a competing risk.

5.7.9 Disease-free Survival

Kaplan-Meier curves will be constructed to estimate Disease-Free Survival (DFS) probabilities for each treatment group using the Primary Efficacy Analysis Population, and 95% CIs will be provided at 18 months. The HR, along with 95% CIs, will be estimated from a stratified Cox model with treatment as a covariate, with strata based on the variables used to stratify the randomization.

5.7.10 Overall Survival

Kaplan-Meier curves will be constructed to estimate OS probabilities for each treatment group using the Primary Efficacy Analysis Population, and 95% CIs will be provided at 18 months. The HR, along with 95% CIs, will be estimated from a stratified Cox model with treatment as a covariate, with strata based on the variables used to stratify the randomization.

5.7.11 Patient Reported Outcomes

Scores for each domain will be summarized by assessment time point and treatment arm using the sample mean, median, range, and quartiles. A variety of strategies for analyzing PRO outcomes and comparing between treatment arms will be examined, including analyses conditional on being alive (using the inverse probability-weighted independent estimating equations (IPW-IEE) proposed by Kurland and Heagerty (2005)), time to deterioration or death based on defined cut points for deterioration of PRO responses, and longitudinal analyses of changes from baseline using linear mixed models and/or pattern mixture models with multiple imputation and delta adjustment.[29]

5.8 Analysis of Exploratory Endpoints

5.8.1 Current additional Immunosuppression-Free survival

Proportions of participants alive and not needing additional immunosuppression will be described in each group at Day 364 (12 months), Day 532 (18 months), and Day 730 (2 years). These will be compared between arms using generalized estimating equations for repeated binary data, adjusting for the variables used to stratify the randomization.

5.8.2 Immune Reconstitution

Immune reconstitution measurements will be described at each time point using sample means, medians, range, and quartiles. Log transformation may be considered if measurements appear non-normal. Comparisons between groups at each timepoint will be done using two-sample t-tests or nonparametric Mann-Whitney tests as appropriate.

The peripheral blood ratios of T regulatory to T effector (Treg/Teff) cells, Natural Killer (NK) cells and other cellular immune subsets at Pre-Conditioning and Days 3, 14, 28, 99, 196, 364 and 730 post-HCT will be summarized using descriptive statistics at each time point, and compared between treatment groups using Mann-Whitney nonparametric tests. Select immune subsets may also be analyzed using a linear mixed model adjusting for baseline value, time and treatment, as well as a treatment by time interaction term.

5.8.3 Vaccine Response

The changes in vaccine response to TDAP and Pneumococcal vaccines from pre- to post-vaccination will be summarized using descriptive statistics.

5.8.4 Organ Failure

The incidence of definite and probably organ failure through Day 100 will be summarized using descriptive statistics.

5.8.5 Healthcare Utilization

Duration of hospitalization admission, number of readmissions, hospital days, and days requiring escalated level of care will be described using median, range, and inter-quartile range, and compared between arms using Mann-Whitney tests. PRO based summaries of financial burden and cost to participants will be described using mean and SD or frequencies and percents as appropriate and compared between arms at each time point using t-tests or chi-square tests, as appropriate.

5.8.6 Steroid-refractory Acute or Chronic GVHD

Incidence of SR acute or chronic GVHD will be estimated using the cumulative incidence function, treating death and second transplant prior to GVHD as competing risks. Estimates and CIs will be provided at 18 months. Cumulative incidence of SR acute or chronic GVHD will be compared between treatment arms using a Fine and Gray model, adjusting for strata variables used in randomization. Results will be summarized using the subdistribution HR and its associated 95% CI.

5.8.7 Pharmacokinetic Analysis

The PK parameters of C_{max}, t_{max}, C_{min}, and $AUC_{(0\text{-}t)}$, will be calculated from the plasma concentrations of ruxolitinib using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix WinNonlin® (Certara USA Inc, Princeton, NJ). All PK parameters will be summarized descriptively by dose, and study day.

Exposure-response analysis on efficacy and safety endpoints will be evaluated for the dose finding portion and at the end of the Phase III portion. The exposure metrics may be estimated by NCA method above, or via a population PK modeling approach that will be planned and reported separately as determined appropriate.

Appendix A:

HUMAN SUBJECTS

1. Participant Consent

Candidates for the study will be identified as described in Chapter 4 of the protocol. The Principal Investigator or his/her designee at each transplant center will contact the candidates, provide them with information about the purpose of the study and obtain voluntary consent if the candidates agree to participate. The BMT CTN will provide a template of the consent form to each center. Each center will add their NMDP IRB-approved boiler-plate language to the consent and submit it for review by the NMDP IRB. The DCC will verify the adequacy of the consent forms prior to submission to the IRB. The NMDP IRB will provide evidence of IRB approval.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a participant identifier code. The code relaying the participant's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

3. Participation of Women and Minorities

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of leukemia and lymphoma in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

Pediatric participants are not able to be included in this study, for three main reasons:

1. The use of PBSC as a graft source is uncommonly used in pediatric centers. As this study requires use of PBSCs, inclusion of pediatric participants would be an accrual barrier.
2. The use of RIC regimens in children with good performance status and limited comorbidities for the indications required for eligibility is uncommon in pediatric participants.
3. Though ruxolitinib is approved in use of participants age 12 and older, the safety data is unknown when using ruxolitinib in combination with Tac/MTX, as earlier studies using Tac/MTX/Ruxolitinib did not allow pediatric participants.

Appendix B:

LABORATORY PROCEDURES

1. Collection of Research Samples for Protocol-Defined Correlative Studies

Pharmacokinetic and Immune Reconstitution research samples will be collected for participants who consent to the BMT CTN 2203 study. Pharmacokinetic samples will be collected on all 50 run-in patients as well as the first 150 patients receiving ruxolitinib in the Phase III portion of the study. Immune Reconstitution samples will be collected in the first 125 patients of each arm of the Phase III portion of the study. Required research samples for study-specific exploratory endpoints are summarized in Table B.1 below.

2. Collection of OPTIONAL Samples for Future Research

For subjects who consent to future research sample collection in the Phase III portion of the study (first 150 consented subjects in each arm; total of 300 patients), blood and urine biospecimens will be made available to approved investigators for meritorious ancillary correlative laboratory studies with the potential to extend the findings of the current study portfolio.

Once the samples are collected at specified time points, they will either be shipped on the day of collection or aliquoted and stored on site until batch-shipping to the specified lab. The collection and shipment of these blood and urine samples will be tracked. These future research samples are summarized below in Table B.2 below. Detailed procedures regarding specimen collection schedules, sample handling/processing procedures, and shipping instructions can be found in the Research Sample Information Guide for the study.

3. Chimerism Assessment

We will study the proportion of participants with full (at least 95% or more) or mixed (5.0-94.9%) total donor chimerism or graft rejection (less than 5% total donor chimerism).

Chimerism analysis will be performed according to institutional practice, with the following as prioritization for analysis:

1. Sorted peripheral blood lymphocyte and myeloid populations
2. Unsorted peripheral blood mononuclear cell populations
3. Whole (unsorted) bone marrow

Table B.1: Required Laboratory Procedures

Purpose	Sample Type	Sample Collection Summary	Dates Samples Obtained	Shipping Specifications	Shipping Location
PK Sampling	4mL Peripheral Blood	Collect blood sample and place 4 mL into a lavender top (K2EDTA) Vacutainer® tube. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant. Place collection tube in ice/water bath. Within 45 minutes of blood collection, place tube(s) in a refrigerated centrifuge (4C) at approximately 1300-1500g for 10 minutes. Transfer equal volumes of plasma into two pre-labeled cryovials (approx. 1mL each) and store at -80 until shipment to central biorepository.	**Safety Run-in (50 pts)** **Cycle 1 Day 3 ±1:** Predose (within 90 minutes of receiving rux) 1-hour post-dose (+/- 15 min) 2 hours post-dose (+/- 30 min) 4-6 hours post-dose **Cycle 1 Day 21 ±7:** Predose (within 90 minutes of receiving rux) **Phase III Rux Arm (150 pts)** **Cycle 1 Day 3 ±1:** Predose (within 90 minutes of receiving rux) 1 hour post-dose (+/- 15 min) **Cycle 1 Day 21 ±7:** Predose (within 90 minutes of receiving rux)	PK samples will be shipped on dry ice in batch as requested by the DCC by priority overnight FED EX delivery.	BMT CTN Research Repository
Immune Reconstitution	5 mL Peripheral Blood	Collect blood sample and place 5 mL into a Streck Cyto-Chex BCT tube. Gently mix sample by inversion 8-10 times to mix.	**Phase III (first 125 pts/arm)** Pre-Conditioning (Day -14 to -7) Day 3 Day 14 (2 weeks) Day 28 (4 weeks, Cycle 2 Day 1) Day 99 (14 weeks, Day 100 visit) Day 196 (Month 8, Day 180 visit/Cycle 8 Day 1) Day 364 (Month 14,12 months post-TX, Cycle 14 Day 1) Day 730 (24 months post-TX)	Blood sample tube will be shipped at ambient temperature on the day of collection to the Kean laboratory by priority overnight FED EX delivery.	Kean Laboratory at Boston Children's Hospital

Table B.2: Optional Future Research Laboratory Procedures

Purpose	Sample Type	Sample Collection Summary	Dates Samples Obtained	Shipping Specifications	Shipping Location
Future Research Whole Blood	6 mL Peripheral Blood	Collect blood sample and place 6 mL into a lavender top plastic BD Vacutainer® tube, containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with EDTA anticoagulant.	Pre-Conditioning (Day -14 to -7) Pre-Infusion (Day -1 to 0) Day 7 (1 week) Day 14 (2 weeks) Day 21 (3 weeks) Day 28 (4 weeks, Cycle 2 Day 1) Day 56 (8 weeks, Cycle 3 Day 1) Day 99 (14 weeks, Day 100 visit) Day 196 (, Day 180 visit/Cycle 8 Day 1) Day 280 (, Cycle 11 Day 1) Day 364 (,12 months post-TX, Cycle 14 Day 1) Day 730 (24 months post-TX) Event Driven (time of aGVHD, cGVHD, relapse or treatment change)	Blood sample tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of whole blood aliquots.	BMT CTN Research Repository
Future Research Serum	10 mL Peripheral Blood	Collect blood sample and place 10 mL into an SST™ tube with Silica Clot Activator & Polymer Gel. Let sample sit upright in rack for 30-60 minutes. **Centrifuge for 10 minutes.** Gel barrier will form separating the serum specimen from clot.	Pre-Conditioning (Day -14 to -7) Pre-Infusion (Day -1 to 0) Day 7 (1 week) Day 14 (2 weeks) Day 21 (3 weeks) Day 28 (4 weeks, Cycle 2 Day 1) Day 56 (8 weeks, Cycle 3 Day 1) Day 99 (14 weeks, Day 100 visit) Day 196 (Day 180 visit/Cycle 8 Day 1) Day 280 (, Cycle 11 Day 1) Day 364 (12 months post-TX, Cycle 14 Day 1) Day 730 (24 months post-TX) Event Driven (time of aGVHD, cGVHD, relapse or treatment change)	Serum blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of serum aliquots.	BMT CTN Research Repository

Purpose	Sample Type	Sample Collection Summary	Dates Samples Obtained	Shipping Specifications	Shipping Location
Future Research PAXgene	2.5 mL Peripheral Blood	Collect blood sample and place 2.5 mL into a single PAXgene Blood RNA Tube. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant.	Pre-Conditioning (Day -14 to -7) Pre-Infusion (Day -1 to 0) Day 7 (1 week) Day 14 (2 weeks) Day 21 (3 weeks) Day 28 (4 weeks, Cycle 2 Day 1) Day 56 (8 weeks, Cycle 3 Day 1) Day 99 (14 weeks, Day 100 visit) Day 196 (Day 180 visit/Cycle 8 Day 1) Day 280 (Cycle 11 Day 1) Day 364 (,12 months post-TX, Cycle 14 Day 1) Day 730 (24 months post-TX) Event Driven (time of aGVHD, cGVHD, relapse or treatment change)	PAXgene RNA blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage.	BMT CTN Research Repository
Future Research PBMC	16 mL Peripheral Blood	Collect blood sample and place 16 mL into BD Vacutainer® CPT tubes, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant prior to centrifugation. **Sample should be centrifuged within 2 hours of collection.**	Pre-Conditioning (Day -14 to -7) Pre-Infusion (Day -1 to 0) Day 7 (1 week) Day 14 (2 weeks) Day 21 (3 weeks) Day 28 (4 weeks, Cycle 2 Day 1) Day 56 (8 weeks, Cycle 3 Day 1) Day 99 (14 weeks, Day 100 visit) Day 196 (Day 180 visit/Cycle 8 Day 1) Day 280 (, Cycle 11 Day 1) Day 364 (12 months post-TX, Cycle 14 Day 1) Day 730 (24 months post-TX) Event Driven (time of aGVHD, cGVHD, relapse or treatment change)	Blood sample tubes will be shipped at ambient temperature on the day of collection to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of PBMC aliquots.	BMT CTN Research Repository

Purpose	Sample Type	Sample Collection Summary	Dates Samples Obtained	Shipping Specifications	Shipping Location
Future Research Urine	5 mL Urine	Collect 5 mL of urine sample and create five 1.0 mL aliquots to be stored at -80ºC. Refer to BMT CTN 2203 Research Sample Information Guide for details related to sample processing, aliquot labeling, storage and shipping.	Pre-Conditioning (Day -14 to -7) Pre-Infusion (Day -1 to 0) Day 7 (1 week) Day 14 (2 weeks) Day 21 (3 weeks) Day 28 (4 weeks, Cycle 2 Day 1) Day 56 (8 weeks, Cycle 3 Day 1) Day 99 (14 weeks, Day 100 visit) Day 196 (Month 8, Day 180 visit/Cycle 8 Day 1)	Frozen urine aliquots will be periodically batch-shipped on dry ice to the BMT CTN Research Repository by priority overnight FED EX delivery. Batch shipping will be directed by the BMT CTN DCC.	BMT CTN Research Repository

Appendix C:

DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

Background – The Sequential Probability Ratio Test

Let $f(\cdot,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0:\theta=\theta_o$ versus $H_1:\theta=\theta_1$ decides in favor of H_1 or H_0 if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i;\theta_1)/f(x_i;\theta_0)$ is the likelihood ratio, and c_α is determined to have the size α. When the sample size is not fixed in advance, further improvement is possible by using Wald's S SPRT. The SPRT continues to sample as long as $B < L_n < A$ for some constant $B<1<A$, stops sampling and decides in favor of H_1 as soon as $L_n > A$, and stops sampling and decides in favor of H_0 as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta=\theta_0$, and of accepting H_0 when $\theta=\theta_1$, respectively, and the expected sample size $E(N\mid\theta_j)=E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0)\le\alpha$ and $\Pr_1(\text{reject } H_0)\le\beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2, \ldots$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1(>\theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities α and β, the SPRT boundaries are given approximately by $A=(1-\beta)/\alpha$ and $B=\beta/(1-\alpha)$. The operating characteristics of the SPRT are given by $O(\theta,\alpha,\beta,\theta_0,\theta_1)=(A^{h(\theta)}-1)/(A^{h(\theta)}-B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int(f(x;\theta_1)/f(x,\theta_2))^{h(\theta)}f(x;\theta)dx=1$.

The formula $E(N;\theta)=[[1-O(\theta)]\log A+O(\theta)\log B]/E(z;\theta)$ provides the average sample number for an arbitrary θ. The sample size distribution is very highly skewed, $Var(N)\approx[E(N)]^2$. Thus, we

will consider a truncated test with maximum sample size of N_0 and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Uncensored Exponential Survival Times

For example, we wish to construct a sequential test for the composite null hypothesis that the rate of NRM at 180 days is less than or equal to 5% versus the alternative hypothesis that it is greater than or equal to 5%. For the derivation of the uncensored SPRT, we will require that the type I error of the test be less than 10%, and that the test provide 90% power to reject the null hypothesis under a specified alternative that the true rate is 10%. A maximum sample size of 250 participants will be permitted.

Let us assume that the survival times, $T_1, T_2, \ldots, T_n$, are completely observed (uncensored) and are i.i.d. with exponential density function $f(T,\theta) = \theta e^{-\theta T}$. These assumptions will be relaxed to incompletely observed data subsequently. In the exponential parameterization, a 180-day survival rate of 95% translates into a mean survival of 9.747 years ($\theta_0 =$ .1026), and 90% translates into a mean survival of 4.746 years ($\theta_1 =$ .2107).

The SPRT is derived with reference to a simple null and alternative hypothesis, in this case, $H_0 : \theta = \theta_o =$ .1026 versus $H_1 : \theta = \theta_1 =$ .2107. However, since the log-likelihood ratio for the exponential, $\log\prod_i^n f(x_i;\theta_1) - \log\prod_i^n f(x_i,\theta_0) = n(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, is a monotone function of $\sum_i^n T_i$, the power of the test is non-decreasing in θ. Thus the SPRT is a one-sided level.10 test of a composite null ($H_0 : \theta \le \theta_o = .1026$) versus a composite alternative ($H_1 : \theta \ge \theta_o = .2107$), with power of $1 - \beta = .90$ at the selected alternative $\theta = \theta_1 =$ .2107.

The SPRT can be represented graphically. The continuation region is bounded by two parallel lines with common slope $(\theta_1 - \theta_0)/(\log\theta_1 - \log\theta_0) =$ 0.150, and intercepts $\log A/(\log\theta_1 - \log\theta_0) =$ 3.05 and $\log B/(\log\theta_1 - \log\theta_0) =$ -3.05 for the lower and upper bounds, respectively. As each individual unit is put on trial and observed to fail, the current sample size, *n*, is plotted against the cumulative sum of failure times. When this graph crosses the upper boundary, the null hypothesis is rejected.

The maximum sample size of 250 participants requires that the SPRT be truncated. We choose to truncate the SPRT by declaring that if the test has failed to terminate after 250 participants, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at a sample size of 250 is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity.

Derivation of a Modified SPRT for Censored Exponential Data

The assumption of uncensored exponential survival times is flawed. However, we consider it reasonable to assume the hazard for NRM is constant over the first 180 days post-transplant, and we will restrict our attention to this time interval. Furthermore, it is not practical to conduct a clinical study by putting each individual on trial and waiting until that individual is observed to fail. We relax our assumptions as follows. Firstly, each individual's time on study will be computed as time from transplant to failure, or to the 180-day time point, whichever comes first. Secondly, we will put individuals on trial as soon as they become available, without waiting for the previous individual to fail.

Let us consider the impact of relaxing these assumptions one at a time. In a fixed sample size trial with uncensored exponential failure times, mean survival time is estimated by the sample mean of the failure times, or total time on study divided by the number of individuals enrolled. When censoring is introduced, the estimate becomes the total time on study divided by the number of observed (non-censored) failures. This suggests that in an exponential SPRT test modified to incorporate censoring, we replace the observed failure times, $T_1, T_2, \ldots, T_n$, with censored failures times, $x_1, x_2, \ldots, x_n$, and the current sample size, n, with the number of observed failures, d.

Now we relax the second assumption and put individuals on trial as soon as they become available, without waiting for the previous individual to fail. Assume that three years are required for accrual of 250 participants to the study, and that the final analysis takes place 180 days after the last participant is entered. Putting all of this together, we propose a modified truncated SPRT, where at any interim time point, s, ranging from 0 to 3 years 180 days, the number of observed failures, *d(s)*, is plotted against the sum of observed time on study, $\sum_i^n X_i(s)$. In practice, monitoring will be scheduled monthly after the start of enrollment to the study. A further modification to the SPRT was to only use the upper boundary for stopping since the primary focus of the monitoring is to protect against unacceptable 180-day NRM rates.

Operating Characteristics of the Modified SPRT Test for Censored Exponential Data

Recall that the uncensored SPRT targeted a drop in NRM-free survival at Day 180 from 95% to 90%, with type I and II errors of 10% and 10%. Since only the upper boundary is used for monitoring, the continuation region of the test was bounded above by a line with a slope of 0.150 and intercept of 3.05. In our example, the sample size is large enough that the reduction in power due to truncation of the test is negligible compared to the increase in power because the modified SPRT, lacking a lower boundary, cannot stop early to "accept" the null hypothesis. In order to maintain type I error, we raise the upper boundary to make it harder to cross. Under the further assumption of uniform accrual over a three-year period, and monthly interim analyses over the course of the study, the operating characteristics of the modified SPRT were obtained from a simulation study. These simulation show that an intercept of 4.02, corresponding to setting parameters α and β to 10% and 10%, result in empirical type I and II error rates of 10% and 10%.

Table C.1: Operating Characteristics of Sequential Testing Procedures from a Simulation Study with 100,000 Replications

True 180-Day Rate	5%	10%
Probability Reject Null	0.095	0.903
Mean Month Stopped	41.0	20.2
Mean # Endpoints in 180 days	11.8	11.6
Mean # Participants Enrolled	240.8	135.4

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true rate of NRM on or before Day 180 was 5%, the test crossed the lower boundary in 9484 of 100,000 replications, for an estimated type I error rate of 9.5%. When the true rate of NRM on or before Day 180 was 10%, the test failed to cross the boundary in the in 9742 of 100,000 replications, for an estimated type II error rate of 9.7%. In this setting, on average, the boundary will be crossed at 20.2 months.

It is interesting to note that the SPRT derived above for exponential failure times with censoring at 180 days, has operating characteristics which are similar to those of a more traditional SPRT, derived for binomial variates with success probability equal to the 180 day failure rate. Using time to failure rather than a simple binary indicator of failure, leads to little improvement in power when failure times are censored relatively soon after entry on study. We speculate that if the constant hazard rate over the first 180 days were high, the exponential test would reject faster than the binomial test but have not conducted simulation studies to demonstrate this.

Appendix D:

KARNOFSKY PERFORMANCE STATUS SCALE

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care.	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

Appendix E:

2014 REFINED DISEASE RISK INDEX[24]

Participating sites to use column labeled as "New DRI Group" to report DRI of enrolled patient.

Disease	Stage	No. of patients	HR*	Original DRI	Percentage of patients	New DRI Group	2-y OS (%)	95% CI
Hodgkin lymphoma CR		126	0.36	Int	14	Low	66	63-68
CLL CR		81	0.47	Low		Low		
Mantle cell lymphoma CR		160	0.51	Int		Low		
Indolent NHL CR		183	0.53	Low		Low		
AML favorable cytogenetics CR		190	0.64	Low		Low		
Indolent NHL PR		276	0.71	Low		Low		
CLL PR		400	0.78	Low		Low		
CML chronic phase 1/2		390	0.82	Low		Low		
CML advanced phase		69	0.92	Int	63	Int	51	50-52
Mantle cell lymphoma PR		149	0.95	Int		Int		
Myeloproliferative neoplasm	Any	426	0.98	Int		Int		
AML intermediate cytogenetics CR		3611	Ref	Int		Int		
ALL CR1		1023	1.00	Int		Int		
T-cell NHL CR		171	1.00	Int		Int		
Multiple myeloma CR/VGPR/PR		339	1.03	Int		Int		
Aggressive NHL CR		181	1.05	Int		Int		
Low-risk MDS adverse cytogenetics	Early†	103	1.06	High		Int		
T-cell NHL PR		164	1.06	Int		Int		
Low-risk MDS intermediate cytogenetics	Early†	516	1.09	Int		Int		
HL PR		225	1.09	Int		Int		
Low-risk MDS intermediate cytogenetics	Advanced†	235	1.18	Int		Int		
Indolent NHL	Advanced†	128	1.21	Int		Int		
CLL	Advanced	265	1.22	Int		Int		
High-risk MDS intermediate cytogenetics	Early	364	1.24	Int		Int		
Aggressive NHL PR		205	1.26	Int		Int		
T-cell NHL	Advanced†	93	1.41	High	20	High	33	31-35
AML favorable cytogenetics	Advanced†	34	1.42	Int		High		
HL	Advanced†	85	1.48	High		High		
High-risk MDS intermediate cytogenetics	Advanced†	179	1.56	Int		High		
High-risk MDS adverse cytogenetics	Early	80	1.58	High		High		
ALL CR2		407	1.58	Int		High		
AML adverse cytogenetics CR		175	1.59	High		High		
Mantle cell lymphoma	Advanced†	46	1.59	High		High		
High-risk MDS adverse cytogenetics	Advanced†	30	1.59	Very high		High		
BL‡ CR		23	1.65	NA		High		
Multiple myeloma	Advanced†	150	1.65	High		High		
ALL CR3		61	1.70	Int		High		
Low-risk MDS adverse cytogenetics	Advanced†	32	1.86	Very high		High		
AML intermediate cytogenetics	Advanced	1227	1.89	High		High		
CML blast phase		52	2.02	Int	4	Very high	23	20-27
ALL	Advanced†	235	2.23	High		Very high		
Aggressive NHL	Advanced†	154	2.54	High		Very high		
AML adverse cytogenetics	Advanced †	76	2.83	Very high		Very high		
BL‡ PR	Advanced †	12	5.21	NA		Very high		

Int, intermediate.
*Hazard ratio for mortality compared with AML intermediate cytogenetics in CR1.
†Advanced stage refers to induction failure or active relapse, including stable or progressive disease for NHL, HL, and CLL.
‡Those categories were not included in the original DRI.

Appendix F:

DIAGNOSIS AND SEVERITY SCORING FOR ACUTE AND CHRONIC GVHD

1. GvHD Clinical Staging

GVHD clinical staging will be according to the MAGIC criteria below

From BMT CTN Technical Document GvHD Guidance v1.0, dated March 13, 2023.

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash < 25% BSA	25-50%	> 50% Generalized erythroderma	Generalized erythroderma (>50% BSA) **plus** bullae and/or desquamation
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl
GI tract	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day	Severe abdominal pain +/- ileus, frank blood or melena (regardless of stool volume)
UGI		Severe/persistent nausea/vomiting/ anorexia			

- For GI GVHD, children is defined as <18 years of age and <50 kg weight
- Upper GI GVHD: in the absence of a biopsy, symptom severity and duration require nausea ≥3 days, and/or ≥ 2 vomiting episodes per day for at least two days, and/or anorexia with weight loss
- For stage 4 GI GVHD, severe abdominal pain is defined as (1) pain that requires opioid use **and** (2) pain that significantly impacts on performance status as determined by the treating physician

Overall Clinical Grade:

Grade 0 No stage 1-4 of any organ

Grade I Stage 1-2 skin and no liver or GI involvement

Grade II Stage 3 skin and/or Stage 1 liver and/or Stage 1 GI

Grade III Stage 0-3 skin with Stage 2-3 liver and/or Stage 2-3 GI

Grade IV Stage 4 in any target organ (skin, liver, GI)

2. Grading of Chronic GVHD (NIH Criteria)[6]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **% FEV1** ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

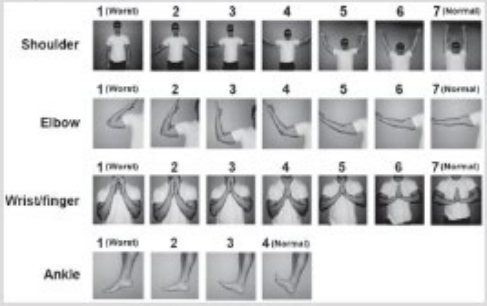
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



3. Categories of Acute and Chronic GVHD

Category	Time of Symptoms after HCT	Presence of Acute GVHD Features	Presence of Chronic GVHD Features*
Acute GVHD			
Classic acute GVHD	≤100 d	Yes	No
Late-onset acute GVHD	>100 d	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

*As defined in Section 4 (below)

4. Signs and Symptoms of Chronic GVHD[6]

Organ or Site	Diagnostic (sufficient to establish the diagnosis of chronic GvHD)	Distinctive (seen in chronic GvHD, but insufficient alone to establish a diagnosis)	Other Features (can be recognized as part of chronic GvHD if diagnosis is confirmed)	Common Features (seen with both acute and chronic GvHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting, or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric)		
Scalp and body hair		• New onset of scarring or non- scarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse, or dull (not explained by other causes) • Premature gray hair	
Mouth	• Lichen-planus like changes	• Xerostomia • Mucocele • Mucosal atrophy • Pseudomembranes • Ulcers		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eyelids with edema)	
Genitalia *Females* *Males*	• Lichen planus-like features • Lichen sclerosus-like features • Vaginal scarring or stenosis • Phimosis or urethral/meatus scaring or stenosis	• Erosions • Fissures • Ulcers		

Organ or Site	Diagnostic (sufficient to establish the diagnosis of chronic GvHD)	Distinctive (seen in chronic GvHD, but insufficient alone to establish a diagnosis)	Other Features (can be recognized as part of chronic GvHD if diagnosis is confirmed)	Common Features (seen with both acute and chronic GvHD)
GI tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea, vomiting • Diarrhea • Weight loss • Failure to thrive
Liver				• Total bilirubin, ALP >2 x ULN ALT> 2 x ULN
Lung	• Bronchiolitis obliterans diagnosed lung biopsy • Bronchiolitis obliterans syndrome*	• Air trapping and bronchiectasis on chest CT	• Cryptogenic organizing pneumonia** • Restrictive lung disease**	
Muscles, fascia, joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis	• Edema • Muscle cramps • Arthralgia or arthritis	
Hemato poietic and immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • AIHA and ITP • Raynaud's phenomenon	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

Appendix G:PATIENT REPORTED OUTCOME QUESTIONS

Following are the Patient Reported Outcome (PRO) survey items for this study. These are presented by assessment, with notes about when each assessment is included on the PRO surveys. Patient-facing PRO documents (paper versions of survey and screenshots of electronic versions) will be created and approved by the NMDP IRB before PRO collection begins.

PROMIS Global Quality of Life

Note: This assessment is included at all PRO time points – baseline, Day 28 (1 month), Day 99 (3 month), Day 196 (6 month), Day 364 (12 month), Day 532 (18 month), Day 730 (24 month).

Please respond to each item by marking one box per row.

	Excellent	Very Good	Good	Fair	Poor
In general, would you say your health is…?	☐	☐	☐	☐	☐
In general, would you say your quality of life is…?	☐	☐	☐	☐	☐

Modified Medical Research Council (mMRC) dyspnea scale

Note: This assessment is included at all PRO time points – baseline, Day 28 (1 month), Day 99 (3 month), Day 196 (6 month), Day 364 (12 month), Day 532 (18 month), Day 730 (24 month).

Please select one phrase that best describes how easy or difficult it is to breathe. *(Select one response)*

- ☐ I only get breathless with strenuous exercise
- ☐ I get short of breath when hurrying on level ground or walking up a slight hill
- ☐ On level ground, I walk slower than people of my age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
- ☐ I stop for breath after walking about 100 yards or after a few minutes on level ground
- ☐ I am too breathless to leave the house or I am breathless when dressing/undressing

Hemmorrhagic Cystitis items

Note: This assessment is included with a 7-day recall period at baseline and Day 28 (1 month), and with a 4-week recall period at Day 99 (3 month) PRO time point.

During the past [7 days or 4 weeks], how many days did you see blood in your urine? *(Select one response)*

- ☐ No days
- ☐ 1 day
- ☐ 2 days
- ☐ 3-5 days
- ☐ 6-7 days

How often did you feel like you needed to empty your bladder right away or else you would have an accident? *(Select one response)*

- ☐ Never
- ☐ One time during the past 7 days
- ☐ 2-6 times during the past 7 days
- ☐ Often once a day
- ☐ More than once a day

Oral Health Impact Profile (OHIP-14)

Note: This assessment is included at Day 532 (18 month) PRO time point.

	Never	Hardly ever	Occasionally	Fairly often	Very often/ every day
Have you had trouble pronouncing any words because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you felt that your sense of taste has worsened because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you had painful aching in your mouth?	☐	☐	☐	☐	☐
Have you found it uncomfortable to eat any foods because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you been self-conscious because of your teeth or mouth?	☐	☐	☐	☐	☐
Have you felt tense because of problems with your teeth or mouth?	☐	☐	☐	☐	☐

	Never	Hardly ever	Occasionally	Fairly often	Very often/ every day
Has your diet been unsatisfactory because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you had to interrupt meals because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you found it difficult to relax because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you been a bit embarrassed because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you been a bit irritable with other people because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you had difficulty doing your usual jobs because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you felt that life in general was less satisfying because of problems with your teeth or mouth?	☐	☐	☐	☐	☐
Have you been totally unable to function because of problems with your teeth or mouth?	☐	☐	☐	☐	☐

Ocular Surface Disease Index (OSDI)

Note: This assessment is included at the Day 532 (18 month) PRO time point.

Have you experienced any of the following during the last week?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
Eyes that are sensitive to light?	☐	☐	☐	☐	☐
Eyes that feel gritty?	☐	☐	☐	☐	☐
Painful or sore eyes?	☐	☐	☐	☐	☐
Blurred vision?	☐	☐	☐	☐	☐
Poor vision?	☐	☐	☐	☐	☐

Have problems with your eyes limited you in performing any of the following during the last week?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
Reading?	☐	☐	☐	☐	☐
Driving at night?	☐	☐	☐	☐	☐
Working with a computer or bank machine (ATM)?	☐	☐	☐	☐	☐
Watching TV?	☐	☐	☐	☐	☐

Have your eyes felt uncomfortable in any of the following situations during the last week?

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
Windy conditions?	☐	☐	☐	☐	☐
Places or areas with low humidity (very dry)?	☐	☐	☐	☐	☐
Areas that are air conditioned?	☐	☐	☐	☐	☐

PROMIS GI - Nausea and Vomiting

Note: This assessment is included at baseline, Day 28 (1 month), Day 99 (3 month), Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Please respond to each question or statement by marking one box.

In the past 7 days, how often did you have nausea—that is, feeling like you could vomit?

- ☐ Never
- ☐ Rarely
- ☐ Sometime
- ☐ Often
- ☐ Always

In the past 7 days, how often did you have a poor appetite?

- ☐ Never
- ☐ Rarely
- ☐ Sometime
- ☐ Often
- ☐ Always

In the past 7 days, how often did you throw up or vomit?

- ☐ Never
- ☐ One day
- ☐ 2-6 days
- ☐ Once a day
- ☐ More than once a day

PROMIS GI - Diarrhea

Note: This assessment is included at baseline, Day 28 (1 month), Day 99 (3 month), Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Please respond to each question or statement by marking one box.

In the past 7 days, how many days did you have loose or watery stools?

- ☐ No days
- ☐ 1 day
- ☐ 2 days
- ☐ 3-5 days
- ☐ 6-7 days

In the past 7 days , how often did you feel like you needed to empty your bowels right away or else you would have an accident?

- ☐ Never
- ☐ One time during the past 7 days
- ☐ 2-6 times during the past 7 days
- ☐ Often once a day
- ☐ More than once a day

PROMIS GI Disrupted Swallowing

Note: This assessment is included at baseline, Day 28 (1 month), Day 99 (3 month), Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Please respond to each question or statement by marking one box per row

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
How often did you have difficulty swallowing solid foods like meat, chicken, or raw vegetables, even after lots of chewing?	☐	☐	☐	☐	☐
How often did you have difficulty swallowing soft foods like ice cream, apple sauce, or mashed potatoes?	☐	☐	☐	☐	☐
How often did you have difficulty swallowing liquids?	☐	☐	☐	☐	☐
How often did you have difficulty swallowing pills?	☐	☐	☐	☐	☐

PROMIS Fatigue 4a

Note: This assessment is included at baseline, Day 28 (1 month), Day 99 (3 month), Day 196 (6 month), and Day 364 (12 month) PRO time points.

Please respond to each question or statement by marking one box per row

During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	☐	☐	☐	☐	☐
I have trouble starting things because I am tired	☐	☐	☐	☐	☐
In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
How run-down did you feel on average?	☐	☐	☐	☐	☐
How fatigued were you on average?	☐	☐	☐	☐	☐

PROMIS Physical Function 8c

Note: This assessment is included at baseline, Day 28 (1 month), Day 99 (3 month), Day 196 (6 month), and Day 364 (12 month) PRO time points.

The following questions are about how you are feeling physically and what you can do. Please respond only thinking about your physical abilities, not including any restrictions to protect your immune system.

Please respond to each question or statement by marking one box per row

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to bend down and pick up clothing from the floor?	☐	☐	☐	☐	☐
Are you able to stand up from an armless straight chair?	☐	☐	☐	☐	☐
Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐	☐	☐	☐	☐
Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
Are you able to wash and dry your body?	☐	☐	☐	☐	☐
Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row

	Not at all	Very little	Somewhat	Quite a lot	Cannot do
Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row

	No difficulty at all	A little bit of difficulty	Some difficulty	A lot of difficulty	Can't do because of health
How much difficulty do you have doing your daily physical activities, because of your health?	☐	☐	☐	☐	☐

PROMIS Cognitive Function 4a

Note: This assessment is included at baseline, Day 99 (3 month), Day 196 (6 month), and Day 364 (12 month) PRO time points.

Please respond to each question or statement by marking one box per row

In the past 7 days…	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
My thinking has been slow	☐	☐	☐	☐	☐
It has seemed like my brain was not working as well as usual	☐	☐	☐	☐	☐
I have to work harder than usual to keep track of what I was doing	☐	☐	☐	☐	☐
I have had trouble shifting back and forth between different activities that require thinking	☐	☐	☐	☐	☐

PROMIS Anxiety 4a

Note: This assessment is included at baseline, Day 99 (3 month), and Day 364 (12 month) PRO time points.

Please respond to each question or statement by marking one box per row

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
I felt fearful	☐	☐	☐	☐	☐
I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
My worries overwhelmed me	☐	☐	☐	☐	☐
I felt uneasy	☐	☐	☐	☐	☐

PROMIS Depression 4a

Note: This assessment is included at baseline, Day 99 (3 month), and Day 364 (12 month) PRO time points.

Please respond to each question or statement by marking one box per row

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
I felt worthless	☐	☐	☐	☐	☐
I felt helpless	☐	☐	☐	☐	☐
I felt depressed	☐	☐	☐	☐	☐
I felt hopeless	☐	☐	☐	☐	☐

PROMIS Satisfaction with Participation in Social Roles 4a

Note: This assessment is included at baseline, Day 99 (3 month), Day 196 (6 month), Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Please respond to each question or statement by marking one box per row

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am satisfied with how much work I can do (including work at home)	☐	☐	☐	☐	☐
I am satisfied with my ability to work (including work at home)	☐	☐	☐	☐	☐
I am satisfied with my ability to do regular personal and household responsibilities	☐	☐	☐	☐	☐
I am satisfied with my ability to perform my daily routines	☐	☐	☐	☐	☐

Modified Lee cGVHD Symptom Scale

Note: This assessment is included at baseline, Day 99 (3 month), Day 196 (6 month), Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Please let us know if you have been bothered by any of the following problems in the past 7 days:

SKIN:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Abnormal skin color	□	□	□	□	□
Rashes	□	□	□	□	□
Thickened skin	□	□	□	□	□
Sores on skin	□	□	□	□	□
Itchy skin	□	□	□	□	□

Please let us know if you have been bothered by any of the following problems in the past 7 days:

EYES AND MOUTH:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Dry eyes	□	□	□	□	□
Need to use eye drops frequently	□	□	□	□	□
Difficulty seeing clearly	□	□	□	□	□
Need to avoid certain foods due to mouth pain	□	□	□	□	□
Ulcers in mouth	□	□	□	□	□

Please let us know if you have been bothered by any of the following problems in the past 7 days:

BREATHING:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Frequent cough	□	□	□	□	□
Colored sputum	□	□	□	□	□
Shortness of breath at rest	□	□	□	□	□

Please let us know if you have been bothered by any of the following problems in the past 7 days:

EATING AND DIGESTION:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Difficulty swallowing solid foods	□	□	□	□	□
Difficulty swallowing liquids	□	□	□	□	□
Vomiting	□	□	□	□	□
Weight loss	□	□	□	□	□

Please let us know if you have been bothered by any of the following problems in the past 7 days:

MUSCLES AND JOINTS:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Joints and muscle aches	□	□	□	□	□
Limited joint movement	□	□	□	□	□
Muscle cramps	□	□	□	□	□
Weak muscles	□	□	□	□	□

Please let us know if you have been bothered by any of the following problems in the past 7 days:

ENERGY:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Shortness of breath with exercise	□	□	□	□	□
Loss of energy	□	□	□	□	□
Need to sleep more/take naps	□	□	□	□	□
Fevers	□	□	□	□	□

Please let us know if you have been bothered by any of the following problems in the past 7 days:

MENTAL AND EMOTIONAL:	Not at all	Slightly	Moderately	Quite a bit	Extremely
Depression	□	□	□	□	□
Anxiety	□	□	□	□	□
Difficulty sleeping	□	□	□	□	□

Income/Insurance (CIBMTR items)

Note: This assessment is included at baseline, Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Which of the following best describes your current job status? *(Select all that apply)*

- ☐ Working full-time (30 or more hours per week)
- ☐ Working part-time (less than 30 hours per week
- ☐ Caring for home or family (not seeking paid work)
- ☐ Unemployed and looking for work (including laid off or furloughed)
- ☐ Unable to work due to illness or disability
- ☐ Retired
- ☐ Student
- ☐ Other, please specify: _____

What kind of work do you do at the present time or in your previous employment? *(Select all that apply)*

- ☐ Management, Business and Financial Occupations
- ☐ Computer, Engineering, and Science Occupations
- ☐ Education, Legal, Community Service, Arts, and Media Occupations
- ☐ Healthcare Practitioners and Technical Occupations
- ☐ Service Occupations
- ☐ Sales and Related Occupations
- ☐ Office and Administrative Support Occupations
- ☐ Farming, Fishing, and Forestry Occupations
- ☐ Construction and Extraction Occupations
- ☐ Installation, Maintenance, and Repair Occupations
- ☐ Production Occupations
- ☐ Transportation and Material Moving Occupations
- ☐ Military Specific Occupations
- ☐ Other, please specify: _____
- ☐ I am not currently and have not previously been employed

Including yourself, how many people live in your household at least 50% of the time?

Adults (age 18 and older): _____

Children (age 17 and younger): _____

What is your total yearly HOUSEHOLD income from all sources, before taxes? *(Select one response)*

This includes money from jobs, disability benefits, social security payments, pensions or retirement, dividends and any other income received by ALL members of your household.

- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $59,999
- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $89,999
- ☐ $90,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $199,999
- ☐ $200,000 or more
- ☐ Don't know

What is your total yearly PERSONAL income from all sources, before taxes? *(Select one response)*
This includes money YOU personally earned from jobs, disability benefits, social security payments, pensions or retirement, dividends and any other income. Do not include income from other household members.

- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $59,999
- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $89,999
- ☐ $90,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $199,999
- ☐ $200,000 or more
- ☐ Don't know

What type of health insurance coverage do you have? *(Select all that apply)*

- ☐ No insurance
- ☐ Medicaid
- ☐ Medicare
- ☐ Medigap
- ☐ Indian Health Service
- ☐ Military-related healthcare
- ☐ Private health insurance (including through your employer)
- ☐ Disability insurance
- ☐ Other government program (please describe): _____
- ☐ Other health insurance coverage (pleas describe):_____
- ☐ Don't know

Work Productivity and Activity Impairment Questionnaire (WPAI)

Note: This assessment is included at baseline, Day 364 (12 month) and Day 532 (18 month) PRO time points.

The following questions ask about the effect of your [PROBLEM] on your ability to work and perform regular activities.

Are you currently employed (working for pay)?

☐ No (skip to page X)

☐ Yes (continue with the questions below)

The next questions are about the past seven days, not including today.

During the past seven days, how many hours did you miss from work because of problems associated with your [PROBLEM]? *Include hours you missed on sick days, times you went in late, left early, etc. because of [PROBLEM]. Do not include time you missed to participate in this study.*

_____ hours

During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____ hours

During the past seven days, how many hours did you actually work?

_____ hours *(if "0", skip to page X)*

During the past seven days, how much did [PROBLEM] affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If [PROBLEM] affected your work only a little, choose a low number. Choose a high number if [PROBLEM] affected your work a great deal.

Consider only how much [PROBLEM] affected productivity while you were working

[PROBLEM] had no effect on work	0	1	2	3	4	5	6	7	8	9	10	[PROBLEM] completely prevented me from working
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

During the past seven days, how much did [PROBLEM] affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If [PROBLEM] affected your activities only a little, choose a low number. Choose a high number if [PROBLEM] affected your activities a great deal.

Consider only how much <u>[PROBLEM]</u> affected productivity <u>while you were working</u>

[PROBLEM] had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	[PROBLEM] completely prevented me from doing my daily activities

Patient-Reported Economic, Income and Insurance Data (PREIID)

Note: This assessment is included at the Day 730 (24 month) PRO time point.

Have you ever taken disability since your stem cell transplant?

☐ Yes
☐ No

If Yes, you have taken disability since your stem cell transplant…

When was the first time you took disability leave after your stem cell transplant? *Please enter the approximate month and year your first leave began.*

Month: _____ Year: _____

How many times have you gone on short-term disability leave since your stem cell transplant? *Short-term disability leave is leave under 3 months.*

☐ Never
☐ 1 time
☐ 2 times
☐ More than 2 times

How many times have you gone on long-term disability leave since your stem cell transplant? *Long-term disability leave is leave over 3 months.*

☐ Never
☐ 1 time
☐ 2 times
☐ More than 2 times

How long was your disability leave in total? *Please include all short-term and long-term leaves you have taken since your stem cell transplant. Please enter '0' if your leave was under 1 month.*

Number of months: _____

How many times have you had to take a less demanding job since your stem cell transplant?

- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ More than 2 times

What was the approximate date you first had to take a less demanding job since your stem cell transplant? *Please provide the approximate month and year.*

Month: _____ Year: _____

How many times have you had to reduce your working hours since your stem cell transplant?

- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ More than 2 times

What was the approximate date you first had to reduce your working hours since your stem cell transplant? *Please provide the approximate month and year.*

Month: _____ Year: _____

What was the approximate date you returned back to your previous normal working hours? *Please provide the approximate month and year.*

Month: _____ Year: _____

- ☐ Never returned back to normal hours

How many times have you been passed over for a career advancement opportunity at your company since your stem cell transplant?

- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ More than 2 times

What was the approximate date you first were passed over for a career advancement opportunity at your company since your stem cell transplant? *Please provide the approximate month and year.*

Month: _____ Year: _____

How many times have you left a job because of your stem cell transplant?

- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ More than 2 times

What was the approximate date you first left a job because of your stem cell transplant? *Please provide the approximate month and year.*

Month: _____ Year: _____

Have you ever returned to work after that?

- ☐ Yes
- ☐ No

What was the approximate date you first returned back to work after you first left a job since your stem cell transplant? *Please provide the approximate month and year.*

Month: _____ Year: _____

Do you believe that you lost income because of complications associated with your stem cell transplant?

- ☐ Yes
- ☐ No

What percentage of your annual income do you think you lost as a result of your complications from your stem cell transplant?

- ☐ 0-5%
- ☐ 5-10%
- ☐ 10-15%
- ☐ 15-20%
- ☐ 20-30%
- ☐ 30-40%
- ☐ 40-50%
- ☐ 50-60%
- ☐ 60-70%
- ☐ 70-80%
- ☐ 80-90%
- ☐ 90-100%

Have you been impacted in any of the following ways because of complications from your stem cell transplant? *Please select all that apply.*

- ☐ Did not seek medical care when required because of financial difficulties
- ☐ Did not take medication at all or at the prescribed dose because of financial difficulties
- ☐ Was evicted from your home because of financial difficulties
- ☐ Was unable to pay your rent because of financial difficulties
- ☐ Needed to find alternative living arrangements because of financial difficulties (e.g., had to move into a relative's home, had to live in your car or a temporary shelter)
- ☐ Inability to pay other non-rent bills
- ☐ None of the above

How would you rate your satisfaction with your current health insurance?

- ☐ Not at all satisfied
- ☐ Partly satisfied
- ☐ Satisfied
- ☐ More than satisfied
- ☐ Very satisfied

How would you rate your satisfaction with your health insurance at the time of your stem cell transplant?

- ☐ Not at all satisfied
- ☐ Partly satisfied
- ☐ Satisfied
- ☐ More than satisfied
- ☐ Very satisfied

Comprehensive Score for Financial Toxicity (COST)

Note: This assessment is included at baseline, Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Below is a list of statements that other people with your illness have said are important. Please mark one response per line to indicate your response as it applies to the past 7 days.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I know that I have enough money in savings, retirement, or assets to cover the cost of my treatment.	☐	☐	☐	☐	☐
My out-of-pocket medical expenses are more than I thought they would be.	☐	☐	☐	☐	☐
I worry about the financial problems I will have in the future as a result of my illness or treatment.	☐	☐	☐	☐	☐
I feel I have no choice about the amount of money I spend on care.	☐	☐	☐	☐	☐
I am frustrated that I cannot work or contribute as much as I usually do.	☐	☐	☐	☐	☐
I am satisfied with my current financial situation.	☐	☐	☐	☐	☐
I am able to meet my monthly expenses.	☐	☐	☐	☐	☐
I feel financially stressed.	☐	☐	☐	☐	☐
I am concerned about keeping my job and income, including work at home.	☐	☐	☐	☐	☐
My cancer or treatment has reduced my satisfaction with my present financial situation.	☐	☐	☐	☐	☐
I feel in control of my financial situation.	☐	☐	☐	☐	☐
My illness has been a financial hardship to my family and me.	☐	☐	☐	☐	☐

Patient-Reported Caregiver Assessment (PRCA)

Note: This assessment is included at baseline, Day 99 (3 month), Day 364 (12 month), Day 532 (18 month) and Day 730 (24 month) PRO time points.

Assistance with activities of daily living can range from a few hours of shopping and cleaning to intensive medical or personal care. Tasks can include shopping, house cleaning, cooking, giving daily living will be referred to as "caregiver" in the following questions.

In the last 3 months to what extent did you rely on someone (ie, caregiver) to assist you with your activities of daily living? *(Select one response)*

- ☐ Never (skip to end of survey, page X)
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always / all the time

Who was the main caregiver who helped you? *(Select one response)*

- ☐ Spouse/partner
- ☐ Parent
- ☐ Son/daughter
- ☐ Sibling
- ☐ Other relative
- ☐ Paid nurse or other healthcare professional
- ☐ Other:_____

In the last 3 months what kinds of help did you require from your main caregiver? *(Select all that apply)*

- ☐ Companionship (eg, talking, reading, keeping company) or supervision
- ☐ Transportation (eg, driving to doctor's appointments, driving for errands)
- ☐ Homemaking (eg, shopping, cleaning, preparing meals)
- ☐ Personal care assistance (eg, feeding, bathing, toileting, dressing, grooming)
- ☐ Healthcare assistance (eg, help with medications, wound care)
- ☐ Managing finances (eg, paying bills, managing budget)
- ☐ Mobility assistance (eg, walking)
- ☐ None of the above

Please answer the following questions if your caregiver was a spouse/partner or any family member.

In the last 3 months, has your caregiver reduced their hours at work? *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Not applicable

In the last 3 months, has your caregiver ever quit their job? *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Not applicable

In the last 3 months, has your caregiver taken early retirement? *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Not applicable

Appendix H:
BMT CTN INFECTION GRADING TABLE AND RECURRENCE INTERVAL DEFINITIONS

From BMT CTN Technical Document Infectious Diseases v2.0, dated September 9, 2024.

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacteremia with skin flora [ex. Coag Neg Staph (CoNS, S. epi), Corynebacterium, or Cutibacterium (Proprioniobacterium)] requiring antibiotics for ≤ 14 days of therapy for treatment Bacterial focus NOS requiring antibiotics for ≤ 14 days of therapy for treatment (e.g urinary tract infection) Bacterial focus NOS requiring only topical, ocular, or otic treatments Cellulitis responding to initial therapy within 14 days Any bacterial pneumonia not requiring supplemental oxygen *C difficile* toxin or PCR positive stool with diarrhea < 1L/day without abdominal pain (child < 20 mL/kg/day)	Bacteremia due to other organisms (not skin flora) Bacterial focus (including bacteremia) with persistent signs/symptoms or persistent positive cultures requiring antibiotics for > 14 days of therapy Cellulitis requiring a change in therapy due to progression or systemic treatment for >14 days Localized or diffuse infections requiring incision with or without drain placement but no debridement Any pneumonia documented or presumed to be bacterial requiring low flow oxygen *C difficile* toxin or PCR positive stool with diarrhea ≥ 1L/day (child ≥ 20 mL/kg/day) or with abdominal pain	Bacteremia with deep organ involvement (e.g. with new or worsening pulmonary infiltrates; endocarditis, brain abscess) Severe shock with bacteremia. Endocarditis Brain abscess or meningitis without bacteremia Active Tuberculosis infection Fasciitis or other skin and soft tissue infection requiring surgical debridement Bacterial pneumonia requiring high flow oxygen or positive pressure ventilation *C difficile* toxin or PCR positive stool with ileus, colon dilation, or toxic megacolon, or need for surgical bowel resection (colectomy, ileostomy)

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Fungal infections	Mucocutaneous candidiasis (excluding esophagitis) (e.g., oral thrush, vaginal candidiasis) and dermatophyte infections (tinea)	*Candida* esophagitis diagnosed by endoscopy Fungal sinusitis confirmed radiologically without orbital, brain or bone involvement. Fungal pneumonia or pulmonary nodules (unless requiring high-flow oxygen or positive pressure ventilation) Fungal skin and soft tissue infection without fungemia, involvement of other sites, or need for debridement *Pneumocystis jirovecii* pneumonia (unless requiring high-flow oxygen or positive pressure ventilation)	Fungemia including candidemia Fungal sinusitis confirmed radiologically with orbital, brain, or bone involvement Fungal pneumonia or pulmonary nodules presumed to be fungal requiring high-flow oxygen or positive pressure ventilation Disseminated infections (defined as multifocal pneumonia with 1 or more additional site of involvement, cutaneous spread, CNS involvement) with any fungus (yeast or mold) *Pneumocystis jirovecii* pneumonia requiring high-flow oxygen or positive pressure ventilation

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Viral infections	Mucosal (mouth, esophagus, vaginal, penile) HSV infection requiring oral antiviral therapy or observation Dermatomal zoster (shingles) affecting ≤ 2 dermatomes Asymptomatic CMV viremia not requiring treatment EBV viremia not requiring treatment Adenoviral infection not requiring treatment HHV-6 viremia not requiring treatment BK viremia or viruria with cystitis not requiring intervention except anti-spasmodics or pain medication Symptomatic upper and lower tract respiratory virus (excludes adenovirus, but includes SARS-CoV-2 [COVID]) not requiring oxygen Viremia (virus not otherwise specified) not requiring therapy	Mucosal (mouth, esophagus, vaginal, penile) HSV infection requiring IV nutrition or IV antiviral therapy VZV infection involving 3 or more dermatomes CMV viremia requiring therapy or CMV viremia requiring a change in therapy due to resistance or with persistent viremia beyond 4 weeks while on treatment EBV viremia requiring institution of therapy Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment HHV-6 infection (e.g., symptoms, cytopenias) requiring treatment BK viremia or viruria with clinical consequence requiring therapy (continuous bladder irrigation, antiviral therapy) and/or surgical intervention Enterocolitis with enteric (GI) viruses Lower tract respiratory viruses (excludes adenovirus, SARS-CoV-2 [COVID]) requiring low flow oxygen SARS-CoV-2 (COVID) infection requiring low flow oxygen Any viremia (virus not otherwise specified) requiring therapy	HSV infection with end organ involvement (encephalitis, hepatic, lung) Severe VZV infection with end organ involvement (coagulopathy, encephalitis, hepatic, lung, eye) CMV end-organ involvement (lung, intestines, eye) EBV PTLD Adenovirus with end-organ involvement, including pneumonitis, but excluding conjunctivitis and upper respiratory tract infections HHV-6 with end-organ involvement (such as encephalitis, hepatitis, pneumonitis) BK viremia or viruria with end organ damage (i.e., renal failure requiring dialysis) Lower tract respiratory viruses (excludes adenovirus, but includes SARS-CoV-2 [COVID]) requiring or high flow oxygen or positive pressure ventilation Any viral encephalitis, meningitis, or end organ disease

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Parasitic infections	Giardiasis or other parasitic gastrointestinal infection with diarrhea <1L / day (<5 episodes / day) (child < 20 mL/kg/day) Chronic strongyloidiasis treated with oral ivermectin or other oral therapies Toxoplasma DNAemia without organ involvement resolving spontaneously (without treatment)	Giardiasis or other parasitic gastrointestinal infection with diarrhea > 1 L / day (5 episodes/ day) (child > 20 mL/kg/day) or with abdominal pain Toxoplasma DNAemia without organ involvement requiring treatment	Strongyloides hyperinfection or disseminated infection CNS or other organ toxoplasmosis
Nonmicrobiologically defined infections	Pneumonia or bronchopneumonia not requiring supplemental oxygen Fever with negative cultures responding to treatment within 14 days Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia requiring low flow oxygen Sepsis without an identified organism (excluding patients receiving immune effector therapy diagnosed with cytokine release syndrome (CRS)) Typhlitis without severe sepsis, ileus, or need for surgical intervention	Any acute pneumonia requiring high flow oxygen or positive pressure ventilation Septic shock without an identified organism (excluding patients receiving immune effector therapy diagnosed with CRS) Typhlitis requiring surgical indication as grade 3

Sepsis (Adult) based on CDC's Sepsis Criteria:

a. Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection.
b. Hypotension: A systolic blood pressure of ≤100 mm Hg or a reduction of >40 mm hg from baseline in the absence of other causes for hypotension
c. Organ Dysfunction defined by Sequential Organ Failure Assessment (eSOFA) score: Any of the following
    i. Initiation of new vasopressor infusion
    ii. Initiation of mechanical ventilation (invasive or non-invasive)
    iii. Acute renal failure (only for patients without end-stage renal failure) defined as **Either:**
        a. Doubling of serum creatinine compared to baseline **OR**
        b. Decrease in estimated glomerular filtration rate (eGFR) by ≥ 50% compared to baseline
    iv. Hyperbilirubinemia defined as **BOTH**
        a. Total bilirubin ≥ 2mg/dl, **AND**

b. Total bilirubin increase of ≥ 50% compared to baseline

v. Thrombocytopenia (only for patients with baseline platelet count >100 cell/μL) defined as **BOTH**
   a. Platelet count <100 cell/μL, **AND**
   b. Decrease in platelet count ≥50% compared to baseline

vi. Serum lactate ≥2 mg/dL

d. Adult Sepsis Criteria: Any organ dysfunction PLUS a source and or suspected source of infection
e. Adult Septic Shock: Sepsis plus vasopressors to maintain adequate blood pressure AND elevated lactate (>2mmol/L or >18 mg/dL).

Disseminated Infections:

Two or more non-contiguous sites infected with the same organisms.

- For infections coded as "Disseminated" per the Infection Form, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.
- It can occur at any level of severity, but most will be grade 2 or 3

Oxygen Supplementation definitions:

a. Low flow: oxygen by nasal cannula at ≤ 6L/minute
b. If patient requires supplemental oxygen at baseline (i.e., on 2L/minute) in the outpatient setting, an increase over the baseline oxygen needs (i.e increase to 3L/minute) is required to meet "low flow" definition
c. High flow: oxygen by nasal cannula at >6L/minute
d. Positive Pressure: Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), intubation with mechanical ventilation

Recurrence Intervals to Determine Whether an Infection is the Same or New:

Type of Infection	Recurrence Internal reflects a previously diagnosed Infection
Cytomegalovirus, Herpes simplex virus, Epstein-Barr virus, and Human herpes virus 6 related infections	2 months (< 60 days)
Varicella zoster virus	2 weeks (< 14 days)
Polyomavirus	2 months (< 60 days)
Bacterial, non-*C. difficile*	1 week (< 7 days)
Bacterial, *C. difficile*	1 month (< 30 days)
Yeast infections (non-cryptococcal)	2 weeks (< 14 days)
Invasive mold infections, dimorphic fungal infection, and cryptococcal infection	3 months (< 90 days)
Helicobacter pylori infection	1 year (< 365 days)
Respiratory viruses: Adenovirus, Enterovirus, Influenza A &B, Respiratory syncytial virus, Parainfluenza, Rhinovirus, and SARS-CoV-2 infections	3 months (<90 days)
Parasitic infections (excluding chronic strongyloidiasis)	3 months (< 90 days)
Chronic strongyloidiasis (defined as positive serologies without detection of larvae)	2 years

Definitions For Invasive Fungal Disease

Invasive fungal disease (IFD) due to yeasts, yeast-like fungi, and dimorphic fungi

IFD type	Criteria for proven IFD	Criteria for evidence of IFD
Endemic mycoses (for example *Coccidioides*, *Blastomyces*, *Histoplasma*)	*At least one of these criteria:* • Histopathology or direct microscopy of specimens obtained from an affected site showing the distinctive form of the fungus, *or* • Culture of the fungus from blood or specimens from an affected site	Clinical diagnosis (pulmonary, cutaneous, osseous, GI, and/or CNS) and initiation of treatment for endemic mycosis *Plus at least one of these criteria:* • *Histoplasma* or *Blastomyces* antigen in urine, serum, or body fluid • Antibody to *Coccidioides* in cerebrospinal fluid • Two-fold rise of *Coccidioides* antibodies in 2 consecutive serum samples
Pneumocystis jirovecii pneumonia (PJP or PCP)	Detection of the organism microscopically in tissue, BAL fluid, or sputum using conventional or immunofluorescence staining	Clinical diagnosis of PJP with initiation of treatment • *Plus at least one of these criteria:* • ß-D-glucan (Fungitell®) ≥8 0 ng/L (pg/mL) from one serum sample (if other etiologies for elevated Fungitell have been excluded) • Detection of *Pneumocystis jirovecii* DNA by PCR from a respiratory tract specimen

IFD type	Criteria for proven IFD	Criteria for evidence of IFD
Cryptococcal infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast consistent with *Cryptococcus* species (based on morphology or PCR) • Recovery of *Cryptococcus* by culture of a sample obtained by a sterile procedure from a normally sterile site showing a clinical or radiological abnormality consistent with an infection • Blood culture with *Cryptococcus* • Positive cryptococcal antigen in cerebrospinal fluid or blood	Clinical diagnosis of cryptococcal infection (pulmonary, CNS, cutaneous, disseminated with initiation of treatment *Plus at least one of these criteria:* • Radiographic evidence of meningeal inflammation • Lesion on imaging consistent with cryptococcal disease
Candida and other yeast infection	*At least one of these criteria:* • Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast • Recovery of yeast by culture of a sample obtained by a sterile procedure from a normally sterile site showing a clinical or radiological abnormality consistent with an infection • Blood culture with yeast	*<u>Applies to Candida only</u>* *Candidemia within the previous 2 weeks with at least one of these criteria:* • Radiographic findings consistent with abscesses in liver, spleen, or brain • Meningeal enhancement • Progressive retinal exudates or vitreal opacities on ophthalmologic examination *Plus initiation of treatment and at least one of these criteria:* • ß-D-glucan (Fungitell®) ≥80 ng/L (pg/mL) from one serum sample (if other etiologies for elevated Fungitell® have been excluded) • Positive T2Candida®

Invasive Fungal Disease (IFD) Due To *Aspergillus* And Other Molds

<table>
<tr><td>Proven mold infection</td><td colspan="3">At least one of these criteria:
Histopathologic, cytopathologic, or direct microscopic examination of a tissue specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage
Recovery of a mold by culture of a specimen obtained by a sterile procedure from a normally sterile site (with clinical or radiological evidence of an infection), excluding BAL fluid, sinus specimens, and urine
Blood culture that yields a mold in the context of a compatible infection
Identification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue</td></tr>
<tr><td>Probable mold infection</td><td><u>Clinical feature</u>
Pulmonary aspergillosis and other pulmonary mold infections
At least one of these patterns are seen on CT imaging:
Dense, well-circumscribed lesions
Air crescent sign
Cavity
Wedge-shaped, segmental, or lobar consolidation
Reverse halo sign (for molds other than Aspergillus)
Aspergillus or other mold tracheobronchitis
Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopy

Aspergillus and other mold sino-nasal disease
At least one of these criteria:
Acute localized pain
Nasal ulcer with black eschar
Extension from the paranasal sinus across bony barriers
Aspergillus and other mold CNS infection
Focal lesions or meningeal enhancement on imaging</td><td>AND</td><td><u>Mycologic evidence</u>
Aspergillus or other mold recovered by culture from sputum, BAL, bronchial brush, or aspirate
Microscopic detection of mold from sputum, BAL, bronchial brush, or aspirate
At least one of these criteria applied to Aspergillus galactomannan antigen:
Single serum or plasma: ≥ 1.0
BAL fluid: ≥ 1.0
Single serum or plasma: ≥ 0.7 plus BAL fluid ≥ 0.8
CSF: ≥ 1.0
At least one of these criteria applied to organism specific PCR (e.g., Aspergillus or Mucor):
Plasma, serum, or whole blood: 2 or more consecutive PCR tests positive
BAL fluid: 2 or more PCR tests positive
At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid</td></tr>
</table>

Appendix I:

ANTICIPATED TOXICITIES

The purpose of this appendix is to outline those anticipated AEs that commonly occur in the population being studied for this trial. The following is a list of events that the Sponsor considers to be common toxicities for agents used in the HCT participant population and toxicities that are known for the HCT process itself. The events listed below require reporting via the Toxicity CRF in Advantage eClinical. Events reported on the toxicity form that also meet the criteria of an SAE will be reported on the AE form set per section 4.7.4 of the protocol. Anticipated events that are listed in this appendix will not be reported individually to the FDA as SUSARs, regardless of relationship assessment per section VI.A of the FDA guidance entitled “Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies”.

General Disorders
Fever
Fatigue
Generalized edema

Immune System Disorders
Allergic reaction
Anaphylaxis

Gastrointestinal Disorders
Mucositis
Nausea
Vomiting
Diarrhea
Pancreatitis
Anorexia

Renal and Urinary Disorders
Cystitis noninfective
Acute kidney injury
Chronic kidney injury

Hemorrhagic Disorders
Hemorrhage

Blood and Lymphatic System Disorders
Neutropenia
Anemia
Thrombocytopenia
Thrombotic thrombocytopenic purpura
Thrombotic microangiopathy

Vascular Disorders
Thromboembolic event

Respiratory, Thoracic, and Mediastinal Disorders
Hypoxia
Dyspnea
Pleural effusion

Hepatobiliary Disorders
Hepatitis
Liver failure
ALT
AST
Bilirubin
Alkaline phosphatase

Cardiac Disorders
Hypotension
Hypertension
Cardiac arrhythmia
Myocardial infarction
Left ventricular systolic dysfunction
Pericardial effusion
Pericarditis
Restrictive cardiomyopathy

Nervous System Disorders
Dizziness
Headache
Neuropathy
Reversible posterior leukoencephalopathy syndrome (RPLS/PRES)
Somnolence
Seizure

Musculoskeletal and Connective Tissue Disorders
Avascular necrosis
Myalgia
Osteoporosis
Arthralgia

Metabolism and Nutrition Disorders
Hyperglycemia

Appendix J:

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