Document Coversheet

Study Title: A Phase II Trial of Haploidentical Allogeneic Stem Cell Transplantation Utilizing Mobilized Peripheral Blood Stem Cells

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PROTOCOL TITLE:

A Phase II Trial of Haploidentical Allogeneic Stem Cell Transplantation Utilizing Mobilized Peripheral Blood Stem Cells

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List of Abbreviations

AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
BM	Bone Marrow Stem Cell Transplant
BMT	Blood or Marrow Transplantation
BU	Busulfan
CLL	Chronic Lymphocytic Leukemia
CMV	Cytomegalovirus
CY	Cyclophosphamide
DLI	Donor Lymphocyte Infusion
DLT	Dose Limiting Toxicity
DVT	Deep Vein Thrombosis
EBV	Epstein Barr Virus
FK506	Tacrolimus
FLU	Fludarabine
G-CSF	Filgrastim (filgrastim-sndz or other approved biosimilar)
GM-CSF	Sargramostim
GVHD	Graft-versus- Host Disease
GvL	Graft-versus- Leukemia
GvM	Graft-versus- Malignancy
HSCT	Hematopoietic Stem Cell Transplantation
MDS	Myelodysplastic Syndrome
MM	Multiple Myeloma
MMF	Mycophenolate

MTD	Maximum Tolerated Dose
MUD	Matched Unrelated Donor
NHL	Non Hodgkin Lymphoma
NRM	Non Relapse Mortality
OS	Overall Survival
PBSC	Peripheral Blood Stem Cell
PBSCT	Peripheral Blood Stem Cell Transplant
PMN	Polymorphonuclear Cell
PNH	Paroxysmal Nocturnal Hemoglobinuria
RIT	Reduced Intensity Transplantation
RRT	Regimen Related Toxicity
SOP	Standard Operating Procedure
SOS	Sinusoidal Obstructive Syndrome
TRM	Transplant Related Mortality
VOD	Veno-occlusive Disease

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1 OBJECTIVES

1.1 Primary Objective

- To evaluate the rate of relapse, defined as recurrence of underlying disease or progression of underlying disease, at 1 year in patients who receive haploidentical PBSCs after reduced intensity conditioning and post-transplant cyclophosphamide and tocilizumab (or tocilizumab alternative).

1.2 Secondary Objective

- To evaluate safety including development of acute GVHD and death at 100 days post-transplant, as well as other treatment related toxicities including chronic GVHD, engraftment rate, non-relapse mortality, PFS at one year, and OS at one year, as compared with historical controls.

1.3 Tertiary Objective

- Correlative studies will include chimerism analysis by molecular analysis and evaluation of immune reconstitution by CMV dextramer analysis using flow cytometry.

2 BACKGROUND

In 2002, a Phase I study out of Johns Hopkins Hospital described the outcomes of patients with hematologic malignancies who underwent related haploidentical HLA matched HSCT. Bone marrow was used as the source of the graft and the conditioning was a nonmyeloablative regimen that consisted of fludarabine 30 mg/m2 given for 4 consecutive days and 2 Gy TBI. Post-transplant cyclophosphamide at 50 mg/m2 was administered on Day +3. Most patients in the study also received cyclophosphamide, 14 mg/Kg on Days -6 and -5, in order to improve engraftment. In addition to post-transplant cyclophosphamide, mycophenolate, and tacrolimus were given for GVHD prophylaxis. 80% of patients achieved engraftment. The rates of grades II-IV acute GVHD and III-IV GVHD were 46% and 23%, respectively. 6 of 10 patients were alive at 6.5 months post-transplant and 5 remained in a complete remission.(1)

Subsequently, results from a Phase I/II trial were published by researchers from Fred Hutchinson Cancer Center (FHCC) and Johns Hopkins Hospital (JHH) in which patients with high-risk hematologic malignancies underwent haploidentical HSCT with bone marrow as the graft source. They received the following regimen for conditioning: fludarabine 30 mg/m2 on Days -6 through -2, cyclophosphamide 14.5 mg/Kg on Days -6 and -5, and 2 Gy TBI on Day -1. They received either one or two doses of post-transplant cyclophosphamide on Day +3 or Days +3 and +4. GVHD prophylaxis also included mycophenolate and tacrolimus. The rate of failure to engraft was 13%. Incidence of grades II-IV and III-IV acute GVHD were 34 and 6%. There was a trend toward less chronic GVHD in the patients who received 2 doses of post-transplant cyclophosphamide (5% vs 25%). Day 100 and 1-year NRM was 4% and 15%, respectively. The rates of relapse, PFS, and OS at 3 years were 46%, 40%, and 50% respectively.(2)

The Blood and Marrow Transplant Clinical Trials Network performed multicenter Phase 2 trials using haploidentical HSCT for patients with leukemias or lymphomas who were candidates for HSCT but did not have appropriately HLA matched donors available. Patients received donor bone marrow after being conditioned with cyclophosphamide, fludarabine and 2 Gy TBI. Post-

transplant, they received 50 mg/Kg of cyclophosphamide on Days +4 and +5 as well as mycophenolate and tacrolimus for additional GVHD prophylaxis. Similar to the previously discussed Phase I/II study from FHCC and JHH, the incidence of grades II-IV acute GVHD at 100 days was 32%. 1-year NRM and relapse were 7% and 45%. OS and PFS at 1 year were 62% and 48%, respectively.(3)

Based on the results of these studies and others, our current practice within the bone marrow transplant program at the Roswell Park Cancer Institute is to consider related haploidentical HSCT using bone marrow as a graft source in patients with advanced or high-risk hematologic malignancies who do not have a 10/12 or better matched HLA donor. We also consider haploidentical HSCT for patients in whom comorbid conditions increase the risk of treatment related toxicities and NRM with our standard reduced intensity conditioning regimen (fludarabine and melphalan and total body irradiation) and matched related or unrelated peripheral blood HSCT. The decision to perform haploidentical HSCT must additionally factor in the relatively high rate of disease relapse; for this reason, we strongly prefer that morphologic CR (at least) be attained prior to haploidentical HSCT. The conditioning regimen we utilize currently is based on the protocol developed at JHH, namely: fludarabine 30 mg/m2/day on days -6 through -2, cyclophosphamide 14.5 mg/Kg/day on Days -6 and -5, and total body irradiation of 200 cGy on day -1, followed by HSC infusion on Day 0. GVHD prophylaxis is with cyclophosphamide 50 mg/Kg/day on Days +3 and +4, as well as mycophenolate from Day +5 through +35, and tacrolimus beginning Day +5. G-CSF is started on Day +5.

The outcomes seen with haploidentical HSCT utilizing post-transplant cyclophosphamide are leading to a shift in the clinical practice within the field of bone marrow transplantation, such that this is a treatment modality that is increasingly being considered as a therapeutic option. Although Phase III randomized studies comparing haploidentical and matched unrelated donor HSCT have yet to be performed, retrospective studies based on data collected from the Center for International Blood and Marrow Transplant Research suggest that rates of acute and chronic GVHD are less with haploidentical HSCT as compared with MUD HSCT and that OS is similar for adult patients with both AML and lymphomas.(4, 5)

Utilization of bone marrow as the graft source is challenging due to several issues. The first is logistical, in that the bone marrow harvest occurs in the operating room and therefore is time consuming to coordinate as compared with peripheral blood stem cell collection. Secondly, undergoing a bone marrow harvest is relatively more difficult for the donor as compared with peripheral blood stem cell collection. Thirdly, the targeted nucleated cell dose is sometimes unable to be obtained during bone marrow harvests, due in some cases to disparities between the donor and recipient weights.

Recently, encouraging data have emerged on the use of peripheral blood stem and progenitor cells (PBSCs) as a graft source for haploidentical HSCTs. In a prospective study including 55 patients who received related haploidentical PB HSCT utilizing fludarabine, cyclophosphamide and TBI conditioning, as well as post-transplant cyclophosphamide, as previously described(2, 3), the incidences of severe acute (grades III to IV) and chronic GVHD in recipients of haploidentical PBSCs were 8% and 18%, respectively.(6) Two-year incidences of NRM, relapse and OS were 23%, 28% and 48%, respectively.

In a separate study of 18 patients receiving PB HSCT, with the fludarabine/cyclophosphamide/total body irradiation conditioning regimen(2) the incidence of

grades I-IV acute GVHD was 53%; the incidence of grades III-IV acute GVHD was 17%. The 2-year incidence of chronic GVHD was 8%. 1-year incidences of NRM, relapse-free survival, and OS were 17%, 53%, and 62%, respectively.(7)

In another, retrospective study including recipients of haploidentical PBSCs, mostly with lymphoid malignancies, the incidences of grade II-IV acute GVHD, severe acute (grades III-IV) and chronic GVHD were 33%, 14% and 13%, respectively.(8) The 2 year incidences of NRM was 12%. No differences in OS (68% at 2 years) or PFS (62% at 2 years) was seen between the recipients of haploidentical PB HSCs and the comparator cohort that received haploidentical BM as a source of HSCs.

Given the promising results of these studies and others(9), we have designed a Phase II trial in which patients with high risk hematologic malignancies will receive related peripheral blood haploidentical HSCT. We plan to utilize the JHH regimen as the chemotherapeutic backbone. For GVHD prophylaxis, we plan to use cyclophosphamide, as well as mycophenolate and sirolimus. Our choice of sirolimus is on the basis of recent data from JHH that suggests sirolimus may be less nephrotoxic than tacrolimus in this setting.(10) In the unexpected situation in which a patient is unable to tolerate oral medications, IV tacrolimus will be administered instead of sirolimus (which cannot be administered intravenously). If tacrolimus is utilized in lieu of sirolimus, it will be dosed and levels will be monitored as per Roswell Park guidelines.

The goal of this study is to determine whether the use of PBSCs for haploidentical HSCTs can reduce the rates of relapse without increasing rates of GVHD. We will compare relapse rates to those we have seen in our own transplant program with the use of BM haploidentical HSCTs; namely about 10% at one year for those in CR at the time of transplant and about 50% for those who are not in CR at the time of transplant.

Cytokine release syndrome (CRS), characterized by fevers, vascular leak, hypotension, and respiratory and renal compromise, in the context of elevated levels of inflammatory cytokines, is a complication that is commonly seen in recipients of peripheral blood haploidentical HSCT due to a higher dose of donor T cells as compared with BM haploidentical HSCT. Tocilizumab, a monoclonal antibody that targets interleukin 6 (IL-6), a key mediator of CRS, has been shown in a retrospective cohort study and a case study to be safe and well tolerated in the treatment of CRS in recipients of peripheral blood haploidentical HSCT.(11, 12) Data were encouraging in regard to efficacy for treatment of CRS, with a resolution of symptoms in 7 of 7 patients who were treated with tocilizumab; a Phase II clinical trial of prophylactic tocilizumab to mitigate the risk of CRS in patients undergoing haploidentical peripheral blood HSCT is ongoing. In an attempt to prevent CRS in this study, we will incorporate a prophylactic dose of tocilizumab on the first day after transplant. (Our BMT program is currently utilizing tocilizumab as standard (non-protocol) prophylaxis against CRS for patients who are at high risk for this syndrome). Siltuximab, a monoclonal antibody that targets IL-6, can be used a second line therapy for CRS or for Immune effector cell-associated neurotoxicity syndrome (ICANS) and CRS presenting together(13, 14). Siltuximab can be used as an alternative when tocilizumab is unavailable.

Inclusion criteria and exclusion criteria are delineated below but importantly both patients in CR and not in CR, (as defined by morphological studies, cytogenetic, molecular and imaging studies as pertinent to the particular disease), are eligible. However, patients in CR with hematologic malignancies and those with bone marrow failure disorders or non-malignant hematologic or immune disorders should not have a 6/6 HLA matched sibling donor available or a 12/12 HLA

matched (including permissively mismatched at DP (10/12 or 11/12 HLA matched with permissive mismatches at DP are considered as similar to 12/12 HLA matches)) unrelated donor available (while availability of a lesser HLA matched donor is acceptable) whereas patients who are not in CR with hematologic malignancies should not have a 6/6 HLA matched sibling donor available or a 10/12 HLA matched (or better HLA matched) unrelated donor (while availability of a lesser HLA matched donor is acceptable. The rationale for these requirements is that there is a higher incidence of relapse with haploidentical HSCT as compared with myeloablative as well as reduced intensity sibling and (matched/mismatched) unrelated peripheral blood HSCT, and the risk of relapse is further increased when patients undergo HSCT without having attained a complete remission. Therefore, for patients who are not in CR at the time of transplant, we are willing to accept a higher risk of GVHD given a relatively high risk of relapse. For patients with hematologic malignancies who are in CR at the time of transplant, we are less willing to accept the increase in risk of GVHD development that occurs with a less than fully HLA matched donor; this holds true for patients with bone marrow failure and with non-malignant hematologic or immune disorders. In some clinical situations, as aforementioned, clinicians prefer haploidentical HSCT for patients in whom comorbid conditions increase the risk of treatment related toxicities and NRM from acute and chronic GVHD with a matched related HSCT or a MUD. For this reason, patients in CR may be enrolled on this study despite having an HLA matched related or unrelated donor, if the treating clinician has concerns about an above average risk of NRM for the patient with a sibling 6/6 HLA matched or unrelated 12/12 HLA matched PB allogeneic HSCT. In addition, patients who are not in CR may be enrolled on this study despite having a sibling 6/6 HLA matched or unrelated 10/12, 11/12 or 12/12 HLA matched donor, if the treating clinician has concerns about an above average risk of NRM for the patient with a 10/12 or better HLA matched PB allogeneic HSCT. Given that most studies to date have not included unrelated haploidentical donors; we will limit the current study to include only related haploidentical donors.

Depending upon the outcome of this study, our strategy for haploidentical hematopoietic stem cell transplant could change. If we find that haploidentical PBSCT is reasonably efficacious and well tolerated, it may replace haploidentical BMSCT; this change would diminish logistical and timing concerns that are sometimes impediments to moving forward efficiently with HSCT.

2.1 Indications for Allogeneic HSCT in Various Disease States

Allogeneic HSCT has an established role in therapeutic strategies for acute and chronic leukemias, bone marrow failure states (aplastic anemia, paroxysmal nocturnal hemoglobinuria, and myelodysplastic syndromes), lymphomas, myeloma, second transplant and immunodeficiencies.

2.1.1 Bone Marrow Failure States

Bone Marrow Failure States and other non-malignant hematologic or immunologic disorders requiring transplantation are preferentially treated with RIT rather than conventional myeloablative HSCT. Primary allogeneic HSCT is appropriate for selected patients with severe aplastic anemia, PNH, and related marrow failure disorders, certain congenital platelet or neutrophil disorders, and congenital immunodeficiencies(15-22) and hemoglobinopathies including sickle cell disease and thalassemia.(23, 24) Haploidentical HSCT has shown encouraging results for patients with non-malignant hematologic disorders.(25, 26) Patients with chromosomal breakage syndromes (such as Fanconi Anemia) or Dyskeratosis Congenita can

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tolerate only very low doses of radiation or chemotherapy due to poor DNA repair capacity. These patients will be excluded from this study.

2.1.2 AML

Less than 20% of adults that are ≥ 60 years with AML in first complete remission (CR1) will achieve a 3-year DFS with conventional chemotherapy-based consolidation.(27) While conventional risk factors like cytogenetics and antecedent hematological disorder play a role, age does appear to be an independent variable.(28-30) Patients over the age of 60 to 65 and those with poor functional status have unacceptable TRM with myeloablative transplant. Reduced intensity conditioning (RIT) offers an opportunity to achieve a cure in a subset of these patients with outcomes comparable to standard myeloablative allogeneic HSCT.(31, 32) Non myeloablative conditioning and haploidentical HSCT with post-transplant cyclophosphamide has been associated with similar success in AML patients.(4)

2.1.3 MDS

MDS is incurable except by allo-HSCT. The risk-benefit ratio favors allo-HSCT for patients as soon as they progress to more advanced disease (Int-2 or higher IPSS score).(33) It is estimated that only about 5% of MDS patients are eligible to receive myeloablative allo-HSCT because of age and other exclusions. RIT has allowed for a reduction in TRM in this group of patients and allowed for wider application of allo HSCT as a therapy for MDS. There is data to suggest that the outcomes for patients who undergo haploidentical HSCT for MDS are similar to those who undergo RIT MUD HSCT.(34)

2.1.4 MPDs

The only cure for a myeloproliferative disorder is an allogeneic HSCT, which needs to be balanced against the TRM associated with conventional myeloablative HSCT. RIT has been used in an effort to reduce the TRM in this group of patients.(35-37) Haploidentical HSCT experience for MPD is limited but has been associated with encouraging outcomes.(38, 39)

2.1.5 NHL

Reduced intensity allogeneic transplantation has a definite role in the treatment of defined subgroups of patients with high-risk NHL with or without a prior autologous transplant.(40) Recent retrospective data suggests lower rates of acute and chronic GVHD and similar OS with haploidentical HSCT as compared with RIT MUD PBSCT for adult patients with lymphomas.(5)

2.1.6 Hodgkin disease

HSCT can be rescued by a RIT.(41) Several studies have shown comparable outcomes between RIC MUD PBSCT and haploidentical HSCT.(42-44)

2.1.7 Multiple Myeloma

Durable remissions for multiple myeloma can occur after allogeneic HSCT. Previous experience with standard myeloablative allogeneic HSCT was disappointing due to a high early TRM despite achieving durable remissions for survivors.(45, 46) Reduced intensity transplantation from suitable related and unrelated donors may permit the development of a curative graft-versus-myeloma effect without high TRM.(47-49) The usual approach is to utilize RIT for

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selected younger patients with well-matched donors either right after auto transplant ("auto-allo") or after relapse from an auto-transplant. A Phase III trial has demonstrated improved overall and disease-free survivals in newly diagnosed myeloma for recipients of a hematopoietic stem-cell autograft followed by a stem-cell allograft from an HLA-identical sibling versus a standard tandem autologous transplant.(50) At this time, there is a paucity of data regarding the efficacy of haploidentical HSCT in patients with multiple myeloma or plasma cell leukemia. However, there is some data that suggests it can be an effective treatment for some patients.(51) Patients with amyloidosis will be excluded from the current protocol.

2.1.8 Non-hematologic Malignancy

Patients with solid tumors will be excluded from the current protocol.

2.1.9 Second Allogeneic Transplants

Second allogeneic transplantation is often offered for relapse after a first allogeneic or autologous transplant and for graft failure. Given that most studies of haploidentical HSCT for hematologic malignancies have demonstrated a higher risk of disease relapse and that some studies have shown higher rates of graft failure as compared with matched related or unrelated donor PBSCT, patients will be eligible to enroll on the current protocol for a first allogeneic transplant only but not for a second allogeneic transplant.

2.2 Rationale

During the past five years within our transplant program at the Roswell Park Cancer Institute, we have been utilizing bone marrow as a source of haploidentical donor HSCTs and have observed relapse rates at one year post transplant of ~10% in patients in CR at the time of transplant and of ~50% in patients who are not in CR at the time of transplant. In this Phase II study, we aim to determine whether utilizing PBSCs as a source of haploidentical donor HSCTs can decrease the rate of relapse without increasing the rates of severe acute (grades 3 and 4) GVHD. For all patients, we do not expect that rates of severe acute GVHD should exceed 20%.

2.2.1 Rationale For Regimen Dose Selection

Fludarabine, a purine nucleoside analog is a potent immunosuppressant that will help prevent donor cell rejection by the recipient. Doses range from 120-200 mg/m^2 over 4 or 5 days and this protocol will utilize 30 mg/m^2/ per day x 5 days.

Cyclophosphamide is an alkylating agent that is, on its own, even in doses as high as 50 mg/Kg for four consecutive days, as has been used to treat autoimmune disease, is non-myeloablative.(52) Whereas HSCs are minimally affected by cyclophosphamide owing to high expression of aldehyde dehydrogenase, B and T lymphocytes and NK cells express low levels of this enzyme and are therefore extremely susceptible to the cytotoxic effects of this drug, making it an immunosuppressive agent. Cyclophosphamide will be given over 2 days at a dose 14.5 mg/Kg over 2 days prior to stem cell infusion in combination with fludarabine to help prevent donor cell rejection by the recipient. It will be given again at 50 mg/Kg over 2 days post stem cell infusion in an effort to prevent donor T-cell activation and subsequent GVHD.

Total Body Irradiation (TBI) is considered myeloablative above 500 to 600 centiGray (cGy). There is extensive experience with lower dose TBI with fludarabine in non-myeloablative conditioning,

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usually at 200 cGy. This dose of radiation, in combination with the aforementioned doses of fludarabine and cyclophosphamide, is considered to be non-myeloablative(53, 54) and therefore, is a regimen that is considered unlikely to generate excess TRM. TBI will be used prior to stem cell infusion in this regimen in order to clear the marrow space to enable engraftment of donor cells.

3 INCLUSION AND EXCLUSION CRITERIA

3.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Any disease that is considered transplant eligible per TCT standards.
2. Disease response noted (i.e. CR, non-CR, or not applicable): Assessed as per disease specific criteria (see Section 3.5).
3. Suitable related haploidentical donor identified per transplant service.

Recipient should not have HLA antibodies to potential donor. If the recipient does have HLA antibodies to the potential donor, an alternative donor is preferred. However, if there are no suitable alternative donors, the anti-HLA antibodies should be depleted per transplant service guidelines.

- Haploidentical donors that are ABO compatible with the recipient are preferred. Minor ABO incompatibility is preferred to major ABO incompatibility. Major ABO incompatibility between recipient and donor is the least preferred but still acceptable for this study.
- It is preferred that the haploidentical donor must be available to donate on day -1 and day 0 at RPCI, so that fresh product can be processed by the RPCI Stem Cell Lab and administered to the patient on day 0. While less preferable, cryopreserved product may be utilized on this protocol.

4. Age ≥ 4 (age ≥ 1 once the Oishei Children's Hospital BMT unit is open) and ≤ 80 years.
5. Have the following clinical laboratory values:
   - Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) > 40% predicted, corrected for hemoglobin and/or alveolar ventilation.
   - Cardiac: left ventricular ejection fraction > 40%.
   - Bilirubin, liver alkaline phosphatase, SGOT or SGPT ≤ 3 x upper limit of normal.
   - Calculated creatinine clearance> 40 cc/min by the modified Cockroft-Gault formula for adults or the Schwartz formula for pediatrics (refer to **Appendix I**).
6. Have a Karnofsky (adult) or Lansky (for ≤16 years) performance status ≥ 60% (refer to Appendix A).
7. Patient must be able to pass Radiation evaluation (i.e.: able to receive 200 cGy).
8. Patients who have failed a prior autologous transplant are eligible; however, at least 90 days must have elapsed between the start of this reduced intensity conditioning regimen and the last transplant if patient had a prior autologous BMT.

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9. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
10. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.
11. If patient is planned to use a fully matched donor, patient is excluded from trial; patient must be planned to undergo a haploidentical matched transplant to participate on study. Patient is still eligible for trial regardless of donor options if PI feels that haplo transplant is in the patient's best interest per clinical decision.

Refer to **Appendix B** for the ***ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA*** checklist.

3.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Participants who have had chemotherapy (not including molecularly targeted agents; examples include, but are not limited to, tyrosine kinase inhibitors such as FLT3 inhibitors and IDH2 inhibitors), radiation treatment and/or surgery 7 days prior to starting conditioning regimen. Those who have not recovered sufficiently from adverse events due to agents administered more than 2 weeks earlier are also ineligible. Exceptions may be made on a case-by-case basis after discussion with the PI.
2. Uncontrolled CNS disease (for hematologic malignancies) per PI discretion.
3. Child-Pugh class B and C liver failure (refer to Appendix J).
4. Concomitant active malignancy that would be expected to require chemotherapy within 3 years of transplant (other than non-melanoma skin cancer). Exception would include any concurrently existing malignancy that could be treated with a transplant per PI discretion. (Example: Patient has AML but a history of mastocytosis.)
5. Uncontrolled diabetes mellitus, cardiovascular disease, active serious infection or other condition which, in the opinion of treating physician, would make this protocol unreasonably hazardous for the patient.
6. Known HIV positive.
7. Pregnant or nursing female participants.
8. Patients who in the opinion of the treating physician are unlikely to comply with the restrictions of allogeneic stem cell transplantation based on formal psychosocial screening.
9. Patients with donor specific HLA antibodies with a titer greater than 3000 MFI (whether or not they have undergone a desensitization protocol).
10. Patients who have undergone a prior allogeneic hematopoietic or (other organ) transplant.
11. Treating physician considers the potential HLA haploidentical donor to be ineligible to receive G-CSF, and/or concern on the part of the treating physician for risk of harm to the potential donor with administration of G-CSF, and/or refusal by the potential donor (or donor's guardian) to receive G-CSF.

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12. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.
13. Received an investigational agent within 14 days prior to enrollment. Exceptions made be made on a case-by-case basis after discussion with PI.

Refer to **Appendix C** for the ***ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA*** checklist.

3.3 Special Populations

The following special populations may be included in this study:

- Children ≥ 4 years of age at this time (≥ 1 year of age once the BMT unit of Oishei Children's Hospital of Buffalo is open).

The following special populations are excluded from this study:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Prisoners
- Pregnant women

3.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

3.5 Arm Distribution

If a patient has multiple disease indications for transplant, arm distribution will be determined by the PI on a case-by-case basis. If a patient is transplanted for a disease not mentioned below, the arm distribution will be determined by the PI.

14. Bone marrow failure disorders: All patients will be allocated to the non-CR arm.

15. Non-malignant hematologic and immunologic disorders: All patients will be allocated to the non-CR arm.

16. Acute Leukemias: Those with AML or ALL who meet disease response criteria for a CR or a CRi (complete remission with incomplete neutrophil and/or platelet recovery), regardless of minimal residual disease (MRD) status (see Appendix L), will be enrolled on the CR arm of this study. Patients who do not meet disease response criteria for a CR or CRi will be enrolled on the non-CR arm of this study. The Disease Risk Index (DRI) will be recorded (55),(56).

17. Chronic Myelocytic Leukemia: The disease response criteria utilized for arm distribution will be as per the current NCCN guidelines(57). Regardless of molecular response, patients with a major cytogenetic response will be allocated to the CR arm. Patients with less than a major cytogenetic response will be allocated to the non-CR arm.(58) The DRI will be recorded.

18. Myeloproliferative and Myelodysplastic Syndromes: For myelofibrosis, patients will be allocated to either the CR arm or non-CR arm as per current definitions of disease response.(59) For polycythemia vera, disease response for arm distribution will be assessed as per recommendations from the European Leukemia Network and the International

Working Group on Myeloproliferative Neoplasms Research and Treatment.(60) For CMML, disease response for arm distribution will be determined on the basis of current uniform response criteria.(61) Those with CMML who meet the disease response criteria for a CR or a complete cytogenetic remission will be enrolled on the CR arm of this study.(61) MDS disease response for arm distribution will be assessed on the basis of the IWG response criteria in myelodysplasia.(62) The DRI will be recorded for all myeloproliferative and myelodysplastic syndromes.

19. CLL: Patients will be allocated to either the CR arm or non-CR arm as per Appendix L. Those with CLL who meet disease response criteria for a CR or a CRi will be enrolled on the CR arm of this study. The DRI will be recorded.

20. MM: Patients will be allocated to the CR arm or non-CR arm according to Appendix L (any response less than a CR, including VGPR, will be allocated to the non-CR arm).(63) The DRI will be recorded.

21. Waldenström's Macroglobulinemia: The International Working Group on Waldenström's Macroglobulinemia uniform response criteria will be utilized to assess disease response for corresponding study arm allocation (any response less than a CR, including VGPR, will be allocated to the non-CR arm).(64) The DRI will be recorded.

22. T or B cell Lymphoma (NHL): Disease response and corresponding study arm allocation will be determined as per Appendix L. Those with NHL who meet the disease response criteria for a CR or a CRu will be enrolled on the CR arm of this study. The DRI will be recorded.

23. Hodgkin Disease: Disease response and corresponding study arm allocation will be determined as per Appendix L. Those with Hodgkin disease who meet the disease response criteria for a CR or a CRu will be enrolled on the CR arm of this study. The DRI will be recorded.

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A maximum of 58 evaluable participants at RPCI will be enrolled.

- Accrual target is 30 patients in the CR arm and 28 patients in the non-CR arm.
- The projected accrual per year is approximately 10-15 patients in the CR arm and 7-10 patients in the non-CR arm, and therefore recruitment is expected to be complete within 5 years following the study starting point.
- Subjects will be followed for 12 months after recruitment completion, so total study duration will be 6 years.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Participants will be identified/recruited/screened from patients at the BMT clinic at RPCI and from multi-disciplinary conference discussion.

6 MULTI-SITE RESEARCH

Not applicable.

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7 STUDY TIMELINES

A maximum of 58 participants at RPCI will be enrolled. Accrual is expected to take 5 years, with follow-up for 12 months from the start of investigational treatment and, annually thereafter as per BMT clinic standard of care.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- Relapse rate at 1 year from time of transplant

8.2 Secondary Endpoints

- GVHD incidence (acute and chronic):
    - Acute GVHD at 100 days post-transplant
    - Chronic GVHD at 1-year post-transplant
- Engraftment rate at 1-year post-transplant
- Clinical response: overall survival (OS) at 1-year post-transplant
- Transplant related mortality (TRM) at 1-year post-transplant
- Progression free survival (PFS) at one year from time of transplant

8.3 Tertiary Endpoints

- Chimerism Analysis
    - Myeloid and lymphoid chimerism expressed as a percentage of donor cells at the following time points: Day 30 (± 10 days), Day 100 (± 14 days), and one year (± 14 days).
- Immune Reconstitution
    - Immune reconstitution is evaluated at the following time points: baseline, Day 30 (± 10 days), Day 100 (± 14 days) and one year (± 14 days) by the peripheral blood BMT SOC immunophenotyping panel and by analysis of CMV-specific immunity (CMV dextramer).

9 DESIGN

The study design will be a Kepner-Chang(65) Type II Phase II design that proceeds in two stages and stops early for futility. Patients in complete response (CR) at the time of transplant will constitute one arm of the study and those that are not in a CR at the time of transplant will constitute a separate study arm. At the end of the first stage of accrual, data will be reviewed to decide if the study should be terminated due to unacceptable toxicity, including an unexpectedly high rate of severe acute GVHD by Day 100 post-transplant or an unacceptably high number of deaths at 100 days or less post-transplant.

In the CR arm, a total of 30 patients will be accrued in two stages. In the non-CR arm, a total of 28 patients will be accrued in two stages.

Evaluable patients are defined as patients who do not have disease progression within Day 100 (and who are alive at day 100). Non-evaluable patients will be excluded in regard to primary outcome analysis but not in regard to analysis of secondary outcomes.

Non-evaluable patients may be replaced if the reason that they become non-evaluable is unrelated to disease progression or to an incident unrelated to treatment on this study (for example, involvement in an automobile accident that leads to fatality). Replacement of non-evaluable patients on this study will be as per the discretion of the study PI.

Subjects will be followed for 12 months after recruitment completion.

10 TREATMENT

Duration of treatment: 11 days (from start to completion of chemotherapeutic administration).

10.1 Dosing and Administration

Eligible patients will receive a non-myeloablative conditioning regimen and allogeneic haploidentical (5 of 10 to 7 of 10 HLA matched) related donor hematopoietic stem cell transplant with post-transplant cyclophosphamide as follows:

Conditioning regimen:

- Fludarabine: 30 mg/m^2/day on Days -6 to -2
- Cyclophosphamide: 14.5 mg/kg IV on Days -6 and -5
- Total body irradiation (TBI): 200 cGy on Day -1

Stem cell infusion:

- Hematopoietic stem cell infusion on Day 0

Supportive care:

- Filgrastim (filgrastim-sndz or other approved biosimilar is acceptable): 5 mcg/kg/day beginning Day +5 until ANC >1500/mm3 for 3 consecutive measurements on at least two different days.
    - For patients with hematologic malignancies characterized by monosomy 7 or deletion of a portion of chromosome 7, rather than G-CSF, GM-CSF (granulocyte-macrophage colony stimulating factor) 500 mcg will be utilized for adults and 250 mcg/m^2 for pediatric patients (maximum dose for pediatric patients is 500 mcg). This is due to a theoretical risk of stimulation of underlying malignancy post-transplant.(66)

GVHD prophylaxis:

- Cyclophosphamide: 50 mg/kg IV on Days +3 and +4 (with Mesna; see “treatment plan”)

Sirolimus and Mycophenolate will be administered as follows:

- Sirolimus: Oral 1 mg starting daily on Day +5. The dose will be adjusted to maintain a trough of 5-10 ng/mL.

- Mycophenolate mofetil (MMF) 1000 milligrams orally every 8 hours or 1500 milligrams intravenously every 6 hours beginning Day +5 until Day +35 (± 5 days).

CRS prophylaxis:

- Tocilizumab will be administered intravenously at 4 mg/kg of ideal body weight 24 hours (± 6 hours) post completion of stem cell infusion on Day +1. In the event of a shortage, siltuximab at 11 mg/kg of ideal body weight (rounded to the nearest vial size) would be substituted.

10.2 Treatment Plan

10.2.1 Stem Cell Collection

Fresh (or cryopreserved) peripheral blood stem cells (PBSCs) will be utilized. Donors will receive 10 micrograms/kilogram G-CSF daily subcutaneously, starting on transplant Day -5. The dose will be rounded to nearest vial size if possible (i.e., 300 micrograms or 480 micrograms).

Mobilized peripheral blood stem cells will be collected by apheresis on transplant Day "-1" and again on Day "0", to achieve a minimum target dose of 5 x 10^6 CD34+ cells/kilogram of recipient weight; a maximum of 30 x 10^6 CD34+ cells/kg of recipient weight will be infused into the recipient and excess product, up to a maximum of 50 x 10^6 CD34+ cells/kg, will be stored. These excess cells may be used by the treating BMT physician for treatment of primary or secondary engraftment failure within the first year of their collection. After 1 year, these cells may be used for laboratory-based research projects, as per discretion of the study PI. Newer stem cell mobilizing agents (such as plerixafor) may be substituted or added to filgrastim if they are FDA-approved. PBSCs will be un-manipulated with the exception of red cell depletion. CD3+ and CD34+ cell counts as fractions of the total nucleated cells (TNC) will be determined according to established institutional flow cytometry protocols.

Donor lymphocyte collection: Donor lymphocytes will not be routinely collected using this protocol. When donor lymphocytes are required for clinical reasons, they will be collected and administered on the RPCI donor lymphocyte protocol.

10.2.2 Preparative Regimen

	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4
Fludarabine (mg/m²/day)	30	30	30	30	30						
Cyclophosphamide (mg/kg, IV)	14.5	14.5								50	50
TBI (200 cGy)						200					
Stem Cell Infusion							X				

Fludarabine

- Fludarabine: 30 mg/m^2 (actual body weight) is infused over 30 minutes on Days -6, -5, -4,-3, and -2 (total dose 150 mg/m^2).

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Cyclophosphamide

- Cyclophosphamide: 14.5 mg/kg (ideal body weight, or actual body weight if less than ideal body weight, or adjusted ideal body weight if actual weight is > 125% of ideal body weight) is infused over 2 hours after completion of fludarabine on Days -6 and -5 and, Cyclophosphamide 50 mg/kg (ideal body weight or actual body weight, whichever is less, or adjusted ideal body weight if actual weight is > 125% of ideal body weight) is infused over 2 hours on Days +3 and +4. Mesna 10 mg/kg (ideal body weight or actual body weight, whichever is less, or adjusted ideal body weight if actual weight is > 125% of ideal body weight) will be infused over 15 minutes on Days +3 and +4 at 30 minutes prior to Cyclophosphamide and at 3, 6, and 8 hours post cyclophosphamide.

Total Body Irradiation

- Schedule: On Day -1, a single fraction of 200 cGy will be given.

Total Body Irradiation will be delivered using a nominal photon beam energy of no less than 4 MV. Dynamic or static fields may be used. However, the patient should be entirely included within the dynamic or static treatment field. Lung shields are to be applied in pairs (both AP & PA) with evenly weighted mid-plane dose from each field. When necessary, lung shields can be combined with open (non-shield) fields during the same fraction to achieve the required mid-plane and lung dose. Dose heterogeneity resulting from lung transmission will be assessed using the AAPM Task Group 29/AAPM-Report Number 17, *The physical aspects of total and half-body photon irradiation*.(67)

TBI, 200 cGy, will be delivered as prescribed to mid-plane at the level of the umbilicus or pelvis; whichever region is thicker. Tissue compensators or other devices will be used to optimize dose homogeneity within ± 5 % of the prescribed dose. Dose homogeneity will be assessed at a minimum of mid plane points at: a) head, at largest diameter, b) neck, at the level of thyroid notch, c) chest, at the xiphoid process, d) umbilicus or pelvis, whichever is thicker, e) mid-thigh, and, f) mid-calf. Optional dose points will be located at: g) knee, h) ankle and, i) umbilicus or pelvis, whichever is thinner. In addition, a set of lung shields, or an equivalent device, will be used to ensure that the lungs will receive within 90 to 100 % of the prescribed dose per fraction. The dose rate at the prescription point shall be between 10 cGy and 15 cGy per minute.

Hydration regimens

- Per clinicians' discretion.

Supportive medications

- Medications prior to stem cell infusion in cases of ABO incompatibility and/or cryopreserved donor product may include diphenhydramine and histamine-2 blocker as per the treating clinicians' discretion.
- Antiemetics, antimicrobials, etc. will be used according to BMT standard of care.
- Glucocorticoid therapy prior to Day +5 should be avoided unless a situation arises such that glucocorticoid therapy is considered necessary by the treating physician, as it may cause interference with the efficacy of cyclophosphamide for GVHD prophylaxis.

10.2.3 Allogeneic Stem Cell Reinfusion

On Day 0 donor hematopoietic stem cells will be infused. The minimum PBSC dose is 5 x 10^6 CD34+ cells/kg of recipient weight; the maximum PBSC dose is 30 x 10^6 CD34+ cells/kg of

recipient weight (all PBSCs collected from the donor up to the maximum dose will be infused into the recipient) **(**see **Appendix E).**

10.2.4 GVHD Prophylaxis and CRS prophylaxis

GVHD prophylaxis will be with post-transplant cyclophosphamide, sirolimus and mycophenolate mofetil (MMF). Tacrolimus (IV or oral) or cyclosporine (IV or oral) may be substituted for sirolimus in the case of inability to tolerate oral medications or other intolerance or adverse reaction and dosed per Roswell Park standards (BMT SOP 104). If this is a temporary issue, a transition back to sirolimus will be made once it has resolved; otherwise, the patient may be continued on either tacrolimus or cyclosporine as per physician discretion. Prophylaxis against CRS will be with tocilizumab(11) (or siltuximab if tocilizumab is unavailable).

DAY	**0**	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**	**+8**
Sirolimus*						X	X	X	X
MMF*						X	X	X	X
Cyclophosphamide				X	X				
Tocilizumab/ Siltuximab		X							

*** Continues beyond Day +8 (see text below).**

Sirolimus

- Starting dose will start as 1 mg PO orally daily beginning on Day +5 and thereafter
- The sirolimus dose will be adjusted to target levels between 5-10 ng/mL.
- In the absence of GVHD, sirolimus will continue until Day +100 and then taper with a goal to be discontinued at approximately 6 months post-transplant. In the case of disease recurrence, sirolimus may be tapered off more rapidly and/or starting before Day +100 post-transplant, as per the treating clinician's discretion.

Mycophenolate mofetil (MMF)/ (Cellcept ®)

- The dose will be 1000 milligrams orally every 8 hours or 1500 milligrams intravenously every 6 hours. Determination of intravenous and oral doses was based on pharmacokinetic levels and calculations to achieve total mycophenolic acid area under the plasma concentration-versus-time curve (AUC) between 30 and 60 microgram/milliliter to prevent graft rejection and graft versus host disease(68, 69): we have measured pharmacokinetic levels on the active drug and the inactive metabolite with Dr. G. Fetterly (unpublished data). Thus, the intravenous dosing is higher based on measured levels. The drug is inactivated by the liver and further dose escalation does not result in higher active drug levels, only higher levels of the inactivated metabolite. The reason for the lower oral dose is gastrointestinal intolerance at doses higher than 1000 mg per mg/m^2 every 8 hours.
- The MMF starts on Day +5 and, in the absence of GVHD or recurrent disease, will continue until Day +35 (±5 days) and then stop without taper.

- MMF may be withheld at the discretion of the attending physician for patients with cytopenias or other toxicities that are thought to be related to the MMF. The clinical team should attempt to restart this medication when it is thought to be clinically safe.

Cyclophosphamide

- Cyclophosphamide will be given as 50 mg/kg IV on Days +3 and +4 for GVHD prophylaxis, as described above.

Tocilizumab

- Tocilizumab will be given intravenously at 4 mg/kg of ideal body weight, on Day +1.
- In the event of a shortage, siltuximab given intravenously at 11 mg/kg of ideal body weight (rounded to the nearest vial size) would be substituted and given on Day +1.

10.3 Supportive Care Recommendations

Prior to initiating therapy, placement of a multi-lumen indwelling silastic catheter is required, preferably a non-tunneled 5 lumen catheter.

Patients will receive full supportive care, including transfusions of irradiated blood and blood products, growth factors, antibiotics, anti-emetics, oral care, etc., when appropriate. Drugs administered for treatment of GVHD as well as anti-infective medications used to treat active infections will be recorded in the CRF. Drugs used to prevent GVHD and to prevent infections will not be recorded in the CRF, as these are given as standard of care.

- Mucosal evaluation and care: Mucositis is expected to be mild to moderate with a RIT regimen. Stomatitis and esophagitis due to herpes virus may be confused with drug-induced mucositis and viral cultures should be obtained if clinically indicated. Patients should receive acyclovir according to the RPCI BMT standard operating procedure (SOP) for an allogeneic transplant patient.
- Antifungal prophylaxis: Antifungal prophylaxis will follow the BMT SOP for allogeneic transplant patients.
- Pneumocystis Pneumonia (PCP) Prophylaxis: Anti-PCP prophylaxis should be given according to the RPCI BMT standard operating procedure (SOP) for an allogeneic transplant patient.
- CMV Infections: Surveillance and treatment for CMV will follow RPCI BMT standard operating procedure (SOP) for allogeneic transplant patients. Surveillance for CMV by CMV antigenemia or PCR is required once weekly until day +100 and then PRN (as needed). Patients with positive CMV antigenemia should receive induction and maintenance treatment as per the RPCI BMT SOP. A CMV level of 1 or less may be repeated on the next available weekday before initiating therapy and if negative, the patient may be screened again in a week. Treatment dosing will be adjusted for hematological and renal toxicity. CMV surveillance will start no later than day +21 unless patient has not engrafted.
- For patients who are pancytopenic prior to transplant, antimicrobial screening prophylaxis should continue through the transplant.

- Anti-bacterial prophylaxis: Patients will receive anti-bacterial prophylaxis during the transplant period as per the RPCI BMT SOP.
- Deep Venous Thrombosis (DVT) prophylaxis will follow the RPCI BMT SOP.
- Sinusoidal occlusive syndrome, also known as veno-occlusive disease (VOD) prophylaxis will follow the BMT SOP.

10.4 Treatment Table Summary

	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1	Day +2	Day +3	Day +4	Day +5	Day +6	Day +7	Day +8
Fludarabine (mg/m^2/day)	30	30	30	30	30										
Cyclophosphamide (mg/kg, IV)	14.5	14.5								50	50				
TBI (200 cGy)						200									
Stem cell infusion							X								
Tocilizumab/ siltuximab								X							
Sirolimus**												X	X	X	X
Mycophenolate**												X	X	X	X
Filgrastim *, **												X	X	X	X

* For patients with hematologic malignancies characterized by monosomy 7 or deletion of a portion of chromosome 7, rather than G-CSF, GM-CSF (granulocyte-macrophage colony stimulating factor) will be utilized.

** Continues beyond Day +8.

10.5 Potential Toxicities and their Management

Patients will be managed in the inpatient and outpatient setting per BMT standards of care. Safety will be monitored on an ongoing basis and discussed, graded and recorded in weekly outcome rounds.

10.5.1 Management of Graft Versus Host Disease (GVHD)

Standard measures for prevention and treatment of GVHD will be followed.

- Patients with symptomatic grade 1 acute GVHD of the skin will be treated with topical steroids.
- Grade II or greater acute GVHD will be treated with high dose methylprednisolone 1-2 milligrams/kilogram daily for 10-14 days. The goal will be at 1 mg per kg at 10 days

followed by slow tapering in responders to a maintenance dose of up to 0.25 mg/kg/day, continued for at least 2 weeks from the disappearance of all symptoms of GVHD.

- Sirolimus /MMF will be maintained or increased during active aGVHD. Glucocorticoid refractory GVHD will be treated as per attending physician's discretion and/or BMT SOP.

10.5.2 Regimen-Related Toxicity

Cardiac:
Patients with pre-existing cardiac disease are at significant risk for developing congestive heart failure and arrhythmias. Studies to be obtained when clinically indicated include EKG (to compare voltage to pretreatment EKG), radionuclide ventriculogram, and/or echocardiography.

Cytokine release syndrome, characterized by fevers, vascular leak, hypotension, and possibly by respiratory compromise, renal insufficiency, and neurologic dysfunction, will be treated with a second dose of tocilizumab at a dose of 4 mg/kg (in addition to the first, prophylactic dose given on Day +1, as long as it has been 24 hours since the previous dose), if determined to be severe enough to warrant treatment; in this case, a serum IL-6 level will be obtained and may be serially measured to assess response to treatment.(11) In the event of a tocilizumab shortage, siltuximab at 11 mg/ kg of ideal body weight (rounded to the nearest vial size) would be substituted and given on Day +1.

Renal:
Some of the agents used in this study can cause renal toxicity, which can be minimized by vigorous hydration, avoidance of exposure of multiple nephrotoxic drugs where clinically possible, appropriate drug monitoring and dose adjustment. Kidney damage is usually reversible, but severe cases may require dialysis. See Abboud et al. 2016 for renal dysfunction caused by cytokine release syndrome.

Pulmonary:
"Engraftment syndrome" consisting of hypoxia, pulmonary effusions and/or infiltrates may be seen at the time of donor cell engraftment and should be treated promptly with methylprednisolone 2 milligrams/kilogram daily followed by rapid taper.

Patients with hypoxia or hypoxia with ambulation should be evaluated as soon as possible by CT scan. Whenever possible, histologic confirmation of the diagnosis should be attempted by bronchoalveolar lavage, transbronchial or open-lung biopsy. This would help to exclude infectious causes (cytomegalovirus/fungal) or confirm the diagnosis of hemorrhage. See Abboud et al(11) for respiratory dysfunction caused by cytokine release syndrome.

Hepatic:
Toxicity is expected to be minimal on this protocol. Management of liver toxicity is with continued ursodeoxycholic acid and standard supportive and symptomatic measures. The clinical team should avoid exposure of patients to hepatotoxic agents.

CNS:
Fludarabine can cause weakness, paraesthesias or peripheral neuropathies, visual or auditory impairment, and/or mental status changes such as confusion, agitation, depression, or coma. Some antibiotics, which may be needed to treat infections during the period of low white blood cell counts, can cause VIIIth cranial nerve damage resulting in hearing loss (especially high-frequency tones) and dizziness which may be permanent. To minimize this possibility, antibiotic levels will

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be monitored. See Abboud et al. 2016 for neurologic dysfunction caused by cytokine release syndrome.

Mucositis:
Many patients will experience mild to moderate stomatitis and odynophagia. Adequate pain relief often requires parental narcotics. Prevention requires aggressive oral hygiene as per RPCI BMT SOPs.

Nausea/Vomiting:
Many patients will experience moderate to severe nausea and vomiting. All patients should receive vigorous antiemetic treatment as per RPCI BMT SOPs. At or after neutrophil engraftment, the development of nausea and vomiting must prompt evaluation for GVHD.

Diarrhea:
Most patients will experience moderate to severe diarrhea in the first three weeks, which responds to standard symptomatic therapy. Appropriate studies are needed to exclude infectious causes of diarrhea, especially *C. difficile*. At or after neutrophil engraftment, diarrhea must prompt evaluation for GVHD.

10.5.3 Other Toxicities

Infections:
Viral infections (CMV, EBV, respiratory viruses including RSV, influenza virus and parainfluenza virus, BK virus, adenovirus), fungal infections (candida and mold) and bacterial infections are commonly expected in the setting of an immunocompromised host, chemotherapy administration and delayed immune reconstitution. These will be managed according to the RPCI BMT SOPs.

Hematologic:
Major ABO incompatibility (recipient vs. donor RBCs) or minor ABO incompatibility (donor vs. recipient RBCs) or both may result in severe hemolysis. ABO incompatible transplants will be identified in advance and will be pre-medicated with a histamine-2 blocker and diphenhydramine, according to the direction of incompatibility as per the treating physician's discretion.

All blood products will be irradiated (2500 cGy) to prevent GVHD. Infection prophylaxis and treatment will be given according to RPCI BMT SOPs and standard accepted medical practice. With prophylactic platelet transfusions, the risk of death from hemorrhage is <5%.

Skin:
Generalized erythroderma can occur with painful palms and soles and superficial desquamation at sites of mechanical trauma. Topical steroid creams may provide symptomatic relief. Severe cases may require a brief course (3-5 days) of systemic corticosteroids. Long lasting hyperpigmentation may follow resolution of the erythroderma.

Hair:
Some patients will experience total (reversible) alopecia.

Secondary malignancy:
The cumulative exposure to chemotherapeutic agents and radiation increases the risk of developing leukemia or a second cancer. The incidence of secondary malignancy is approximately 5%.

Failure to engraft:
Autologous count recovery is the most likely outcome because this combination is sub-myeloablative.

Toxicities of G-CSF (donor):
These toxicities may include bone pain, headache and myalgias. These can be treated with non-narcotic and narcotic analgesics. Splenic rupture in donors with an enlarged spleen and precipitation of an acute hemolytic episode in donors with sickle cell trait are rare and need to be evaluated.

Toxicities of Apheresis (donor):
With apheresis the following discomforts may occur: tingling around mouth or in fingers, feeling cold or feeling a pressure sensation in chest due to the blood thinner (sodium citrate), feeling light-headed or fainting any time during or at the end of the procedure, pain, bruising or infection at the point of the needle entry into the skin. A reaction (such as a rash) to a drug is possible if the patient has an unknown allergy. Blood loss (less than a pint) may rarely occur because of equipment problems which make it impossible to return the blood to the donor. Air entering the blood stream causing air to go to body organs (very rare risk because of safety measures used).

11 PROCEDURES INVOLVED

Please contact the Transplant Program Coordinator or Clinical Research Coordinator to enroll patients on the study.

Informed consent: Patient must be aware of the nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and of its consent form is required and will have been obtained before this study open.

Histological review: Submission of appropriate tissue samples or outside histo-pathologic slides to confirm the underlying diagnosis. Remission/relapse status should be confirmed within 30 days, and no later than 60 days before transplant conditioning starts.

Radiological review: All patients with lymphoma/multiple myeloma must have appropriate radiographic workup (CT and/or PET/CT for lymphoma; PET for multiple myeloma (at a minimum)) prior to registration and must be submitted for review.

11.1 Registration

Registration procedures:

- Confirm eligibility criteria for patients (Appendix B and Appendix D) and donors (Appendix D).
- Complete the transplant registration worksheets for patient and donor.
- Record on the flow sheets: patient name, patient identification number, date of birth, patient's gender, disease type and stage, treatment start date, date of signed consent, patient's race/ethnicity. When the patient is registered, a patient identification number will be generated.

- Data pertaining to this protocol will be collected by the BMT research nurses, data coordinators and/ or any other persons assigned by the BMT department head.

Eligibility of each participant will be established prior to enrollment.

Informed consent **MUST** be completed prior to receiving any study related procedures.

11.2 Protocol Date Definitions

On-Study Date	Start Treatment Date	Off-Treatment Date	Off-Study Date
Date of pre-admission clinic visit	Date of conditioning regimen initiation	Date of completion of the last dose of cyclophosphamide	Date of death due to any cause or, until study completion

11.3 Study Observations

(Baseline testing is to be obtained within 60 days of enrollment unless otherwise noted)

- HCT-CI/Age composite score (70).[71]
    - Baseline
- Karnofsky/ Lansky Performance Status:
    - Baseline
    - Weekly after discharge until Day 100 after stem cell infusion
- Temperature:
    - Baseline
    - Day +1 through + 10 (including Day +1 and Day +10)
- Hematology/ Chemistry:
    - Baseline
    - Important hematologic recovery endpoints:
        - The first of 3 consecutive days of absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L
        - Platelets $\geq 20 \times 10^9$/L after 7 consecutive days with no platelet transfusions
        - Day (post stem cell infusion) of last platelet transfusion
- Serology:
    - Baseline: HIV, hepatitis (Hep B virus surface, Ag; Hep B virus core antibody, total; Hep C virus, antibody; only if clinically indicated: HCV RNA, HBV DNA), CMV
- Quantitative immunoglobulins:
    - Baseline
    - Post-transplant SPEP, IFE, Quantitative immunoglobulins, serum beta-2 microglobulin, kappa/lambda free light chains and 24-hour urine for protein electrophoresis and free light chains will be done only for patients with multiple myeloma on Day 100-160 and then as clinically indicated
- Urinalysis (biochemical):
    - Baseline and post-transplant as clinically indicated

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- HLA typing:
  - Baseline (this can be done at any time; does not have to be within 60 days of enrollment)
- Creatinine clearance:
  - Baseline
- Pulmonary function tests (including DLCO):
  - Baseline, Day 100 (±14 days), Day 365 (±14 days), and as clinically indicated.
- MUGA or ECHO:
  - Baseline
- EKG:
  - Baseline
- Bone marrow aspirate/ biopsy (aspirate for molecular, flow, and cytogenetics analysis) will be performed for patients with leukemias and bone marrow failure states only; patients with other malignancies will have BM aspirate and biopsy only if bone marrow was involved previously:
  - Baseline, Day 30 (±10 days), Day 100 (±14 days), at 1 year (±14 days), and then as indicated
    - If the patient is medically unfit or has scheduling difficulty, delay is allowed at all follow-up time points.
  - Unseparated chimerism will be analyzed whenever a bone marrow aspirate is performed after transplant: refer to Section 11.8.1
- Chest X-ray (PA and lateral):
  - Baseline
- PET scan: for patients with myeloma (at baseline).
- Disease Evaluation: CT Scan and/or PET and/or MRI
  - Patients with *lymphoma*: Baseline, Day 100 post stem cell infusion, and 1 year post stem cell infusion (± 14 days). Regions of imaging will be at the discretion of the clinician. Additional imaging studies including CT and/or PET may be performed as clinically indicated.
  - All other patients will have CT and/or PET scans and/or MRI performed as clinically indicated (which may or may not be as part of disease evaluation).
- Peripheral blood for chimerism:
  - Day 30 (±10 days), Day 100 (±14 days), at 1 year (±14 days), and then as indicated: refer to Section 11.7.1.
- Peripheral blood for immune reconstitution: CMV dextramer analysis and BMT SOC flow panel:
  - Baseline, Day 30 (±10 days), Day 100 (±14 days), at 1 year (±14 days) and then as indicated: refer to Section 11.7.2.

11.4 Follow-up Evaluations

The following BMT standard of care lab assessments will be performed at Day 30 (± 10 days), Day 100 (± 14 days) and at 1 year (± 14 days) following transplant:

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- Hematology: CBC with automated differentials
- Chemistry: CMP
- Bone marrow biopsy will be performed for chimerism and engraftment evaluation.

Patients with disease progression or who require a subsequent transplant will not be taken off protocol but will be followed for survival.

11.5 Important Immunologic Recovery Endpoints

- Myeloid and lymphoid chimerism expressed as a percentage of donor cells at the following time points: Day 30 (±10 days), Day 100 (±14 days), and 1 year (±14 days) after stem cell infusion.
- Immune reconstitution will be evaluated by CMV dextramer analysis and the BMT SOC panel (which measures lymphocyte subsets) using flow cytometry at the following time points: baseline, Day 30 (±10 days), Day 100 (±14 days), and 1 year (±14 days) after stem cell infusion.

11.6 Schedule of Procedures and Observations

The schedule of research-related procedures and observations for this study is summarized in **Appendix F**.

11.7 Correlative Studies

11.7.1 Chimerism Analysis

Chimerism analysis is clinically useful and important for this study. After transplant, serial samples of blood and marrow will be analyzed for chimerism analysis as per the Molecular Diagnostic Laboratory SOP. Lineage specific (separate lymphoid and myeloid) chimerism will be analyzed in blood (per BMT SOP) at the following time points: Day 30 (±10 days), Day 100 (±14 days), at 1 year (±14 days), and then at unscheduled intervals until full donor chimerism is attained. Unseparated chimerism will also be analyzed in bone marrow whenever a bone marrow aspirate is performed.

Peripheral blood will be collected in 2 green top tubes for separated chimerism and 1 milliliter of bone marrow aspirate will be collected in 1 purple top tube for non-separated chimerism. Chimerism studies will be performed by the RPCI Molecular Diagnostic lab.

Patients not converting to 100% donor T-cell chimerism by Day + 180 and/or showing signs of progression of disease after sirolimus and MMF withdrawal, and/or with refractory viral infection, will be evaluated for DLI. Patients who have active GVHD will not receive DLI.

11.7.2 Immune Reconstitution

Peripheral blood will be collected (per BMT SOP) at baseline (prior to transplant), Day 30 (±10 days), Day 100 (±14 days), and at 1 year (±14 days) for evaluation of immune reconstitution. Immune reconstitution will be measured by flow cytometry using markers for T cells (CD3, CD4, CD8, γδ, CD45RA, CD45RO, CD27, HLADr, CD31, CD25, CD127), B cells (CD19, CD20,

CD27, CD38, IgD), and NK cells (CD56, CD16), as well as CMV dextramers. Flow cytometry will be performed by the flow cytometry lab under Dr. Paul Wallace's direction.

12 WITHDRAWAL OF SUBJECTS

12.1 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted as per BMT standard of care. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate electronic case report form (eCRF).

Reasons for treatment discontinuation should be classified as follows*:

- Death
- Progressive disease
- Toxicity; treatment related or unrelated
- Investigator judgment
    - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.

* If the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the patient will be removed from protocol treatment and placed on follow-up. In this event the reason for withdrawal will be documented, the PI will be notified and the patient will be followed for toxicity, survival, progression and relapse.

Any patient with disease progression or who requires a subsequent transplant will be placed on survival follow-up. Details including last staging, patient survival, and secondary malignancies should be documented in the eCRF.

13 RISKS TO SUBJECTS

13.1 Fludarabine Monophosphate

- Myelosuppression (dose limiting toxicity), fever, nausea, vomiting, stomatitis, diarrhea, gastrointestinal bleeding, anorexia, edema, skin rashes, myalgia, headache, agitation, hearing loss, transient episodes of somnolence and fatigue, autoimmune hemolytic anemia, autoimmune thrombocytopenia, paresthesias, peripheral neuropathy, renal and pulmonary toxicity (interstitial pneumonitis).
- Severe fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status were encountered almost exclusively after very high doses of fludarabine

monophosphate. Such toxicity has only been rarely demonstrated at the 25-40 milligrams dosage of fludarabine monophosphate.

- Very rarely described complications include transfusion-associated graft versus host disease, thrombotic thrombocytopenic purpura, and liver failure.
- Tumor lysis syndrome, complicating fludarabine monophosphate therapy has been observed, especially in patients with advanced bulky disease.
- Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed in both pre-treated patients receiving fludarabine and in individuals receiving fludarabine combined with other agents (corticosteroids, mitoxantrone, and cyclophosphamide).

13.2 Cyclophosphamide

The most frequently reported adverse events include: nausea/vomiting, cardiomyopathy, rash, mucositis, stomatitis, sterility, diarrhea, hemorrhagic cystitis, edema, alopecia, anemia, hemolysis, leukopenia, alopecia, appetite loss, amenorrhea, thrombocytopenia, anemia, fatigue, pulmonary fibrosis, secondary malignancies including urological malignancies.

13.3 Sirolimus

In patients receiving sirolimus, 23% to 33% experienced anemia, and 14% to 30% experienced thrombocytopenia. Leukopenia has also been reported. Rare cases of microangiopathic hemolytic anemia have been reported. Cases of lymphoproliferative disorders have been reported. Lymphocele development has been reported.

Hypertension has been reported in 49% of patients receiving sirolimus. Antihypertensive therapy may be required. Edema has been reported in 18% to 20% of patients receiving sirolimus. Chest pain, venous thromboembolic disease, and tachycardia have also been reported.

Headaches have occurred in 20% to 34% of patients on sirolimus, pain has occurred in 29% to 33% of patients, and dizziness has also been reported. Gastrointestinal adverse effects of sirolimus have included constipation (36% to 38%), and stomatitis (3% to >20%).

Hypertriglyceridemia has been reported in 45% to 57% of patients taking sirolimus. Amenorrhea, diabetes mellitus, hypermenorrhea, hypervolemia, hypokalemia, elevated lactate dehydrogenase, menstrual disease and ovarian cyst formation have also been reported.

In patients taking sirolimus, 33% have had urinary tract infections. Herpes simplex infection, herpes zoster, pyelonephritis and sepsis have also been reported.

Arthralgia has been reported in 25% to 31% of patients taking sirolimus. Osteonecrosis has also been reported.

A decline in kidney function has been seen in 39% to 40% of patients taking sirolimus.

Epistaxis and pneumonia have been reported in patients who were taking sirolimus.

Other miscellaneous effects that have been noted to occur in patients taking sirolimus include but are not limited to wound healing impairment, skin cancers, interstitial pulmonary disease (including pneumonitis, pulmonary fibrosis, and bronchiolitis obliterans organizing pneumonia), pulmonary alveolitis, pulmonary hemorrhage, reversible posterior leukoencephalopathy syndrome, liver toxicity, and cardiac tamponade.

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13.4 Mycophenolate mofetil

The principal adverse reactions associated with the administration of mycophenolate include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections. Patients receiving immunosuppressive regimens involving combinations of drugs, including mycophenolate, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Over suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen. Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving mycophenolate (2000 to 3000 milligrams daily) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients.

There are no adequate and well-controlled studies in pregnant women. However, as mycophenolate has been shown to have teratogenic effects in animals, it may cause fetal harm when administered to a pregnant woman. Therefore, mycophenolate should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. It is recommended that mycophenolate therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

In patients receiving mycophenolate (2000 or 3000 milligrams) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients.

Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3$ / microliter] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving mycophenolate 3000 milligrams daily respectively. If neutropenia develops (ANC $<1.3 \times 10^3$ / microliter), dosing with mycophenolate should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal transplant patients treated with mycophenolate 3000 milligrams daily. Gastrointestinal perforations have rarely been observed.

Allergic reactions to mycophenolate have been observed; therefore, mycophenolate is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. Mycophenolate intravenous is contraindicated in patients who are allergic to Polysorbate 80 (TWEEN).

13.5 Tocilizumab

Data on the safety of tocilizumab has mostly been in the context of treatment of rheumatoid arthritis, often in combination with other agents; infections have been seen in this setting.(72) However, data on safety of tocilizumab in the post hematopoietic stem cell transplant setting are few, but they suggest that it is well tolerated.(12, 73)

13.6 Siltuximab

Commonly seen risks for siltuximab are: edema (≤26%), localized edema (≤26%), pruritus (28%), skin rash (28%), weight gain (19%), hyperuricemia (11%), and upper respiratory infection (26%).

13.7 Infusion Risks

Stem Cell reinfusion is associated with the following hazards:

- Temporary shortness of breath due to the lodging of small particles in the blood vessels of the lungs may occur. This is a less likely side effect.
- If the bone marrow or stem cells that are to be used have been cryopreserved (frozen), a chemical called DMSO (dimethylsulfoxide) is used during the freezing process. This chemical is used to protect the cells from damage during freezing. DMSO produces an odor on the breath that lasts 1 to 2 days. In rare instances, severe allergic reaction may occur.
- There is also a chance of developing a blood transfusion reaction during the reinfusion of stem cells. The following less likely side effects may occur: chills, back pain, decreased blood pressure, chest pain, and increased rate of breathing. Wheezing, hives, rash, as well as difficulty breathing, and increased heart rate are considered unlikely. Rarely, temporary life support with artificial ventilation is required.
- CRS (cytokine release syndrome) is a potentially life-threatening reaction that may occur hours to days post stem cell infusion. It is caused by high levels of T cell activation and is characterized by high levels of inflammatory cytokines, and clinically manifests with high fevers, and may also involve neurologic dysfunction, nephrotoxicity, cardiovascular and pulmonary compromise. Tocilizumab , an antibody against IL-6, has been successfully used to treat CRS.(11). The alternative siltuximab, is also an antibody against IL-6 that can be used as a second-line treatment for CRS.
- Failure to engraft is a rare complication and it is possible that the recipient's own bone marrow might grow back. A second transplant may be needed.

13.8 Total Body Irradiation

During treatment the most common side effects include:

- Headache
- Nausea and vomiting
- Diarrhea
- Fatigue
- Skin reaction

Less common is swelling of the salivary glands, which can produce pain in front of the ear and in the jaw.

The following may occur after receiving TBI (and may be caused, in part, by any subsequent chemotherapy):

- Hair loss.

- Discomfort in the throat and mouth.
- Change in taste.
- Mouth sores.
- Nausea and vomiting.
- Diarrhea.
- Bone marrow suppression (low blood counts).

TBI can cause long-term side effects. They can occur months or years after your transplant.

- Sterility is an expected side effect. Sexual function and pleasure will not be affected. Please talk to your doctor or nurse about any concerns you have.
- About half of the patients will need thyroid supplements.

Other long-term side effects are rare but can occur. They include:

- Inflammation of the sac that surrounds the heart.
- Inflammation of the lungs.
- Cataracts.
- Second malignancies or new cancers

14 POTENTIAL BENEFITS TO SUBJECTS

There is no direct benefit to the patient.

15 DATA AND SPECIMEN BANKING

Not Applicable

16 MEASUREMENT OF EFFECT

The following criteria will be used for study evaluation:

16.1 Disease Response Criteria

- Please refer to Appendix M and Appendix N for post-transplant response criteria.

16.2 Study Endpoints

- The primary endpoint is relapse rate at one year.

16.3 Engraftment

Neutrophil engraftment is defined as the first day in which ANC is $> 0.5x10^9$/ liter for three consecutive days. Platelet engraftment is the first day that platelets are $> 20\ x10^9$/ liter for seven consecutive days without transfusion support.

Chimerism analysis will be performed at regular intervals. Lineage specific (separate lymphoid and myeloid) chimerism will be analyzed in blood at the following time points: Day 30 (±10 days), Day 100 (±14 days) and then at unscheduled intervals until full donor chimerism is attained.

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Primary engraftment failure is defined as lack of evidence of neutrophil or platelet engraftment at Day +35, confirmed by a bone marrow biopsy showing < 5% cellularity in the absence of persistent malignancy. Late graft failure will be defined as initial neutrophil engraftment by Day +35 documented to be of donor origin followed by a drop in ANC to < 500 for more than three days, independent of myelosuppressive drugs, severe GVHD or infection.

Graft rejection is defined as graft failure with documentation of return of recipient hematopoiesis as determined by cytogenetic/chimerism analysis.

17 SAFETY EVALUATION

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

17.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Reporting Adverse Events

17.2.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4. The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably

explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.3 Reporting Adverse Events:

The following AEs occurring between the start date of intervention until Day +30, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported: New information will be reported after it is received.

- ≥ Grade 3 toxicity by CTCAE version 4 (see Section 17.2), excluding hematologic toxicities
- ≥ Grade 1 but < grade 4 cytokine release syndrome (CRS) by CTCAE version 4 (see section 17.2)
    - ≥ Grade 4 CRS will be reported as a SAE

Additionally, patients will undergo outcome assessment for and grading of acute and/or chronic GVHD weekly for the first 100 days post-transplant, every 3 weeks (± 7 days) from Day 100 through Day 180, and monthly (±14 days) through Day 365 post-transplant.

- Acute GVHD will be graded according to the criteria in Appendix G.
- Chronic GVHD according to the criteria in Appendix H.
- Any histologic evidence of GVHD (from tissue biopsies) will be noted.

Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.4 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).

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- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

For the purposes of this study, the following events will also be considered SAEs:

- ≥ Grade 3 acute GVHD
- ≥ Grade 4 CRS

17.4.1 Reporting Serious Adverse Events

All new SAEs occurring from the start date of intervention until Day +30 will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention, should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to Section 17.6 for details on reporting Unanticipated Problems.

17.5 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.6 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.4.

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17.6.1 Reporting Unanticipated Problems:

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

17.7 FDA Reporting

Not applicable for this study.

18 DATA MANAGEMENT AND CONFIDENTIALITY

18.1 Data Collection

Full build studies are managed by RPCI CRS Data Management for analysis by RPCI Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.2 Maintenance of Study Documents

Essential documents will be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

18.3 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.5 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain

confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

19 STATISTICAL PLAN

The primary objective of this study is to evaluate the rate of relapse, defined as recurrence of underlying disease or progression of underlying disease, at 1 year in patients who receive haploidentical PBSCs after reduced intensity conditioning and post-transplant cyclophosphamide and tocilizumab (or tocilizumab alternative).

The design of this trial will consist of two concurrent two-stage trials with a common endpoint stratified by complete responders and non-responders. (Patients with non-malignant hematologic disorders will be considered as non-responders).

The primary endpoint will be the relapse rate at 1 year. The dates of relapse will be recorded as the date upon which the data to make a diagnosis of relapse was attained (for example, the date upon which a diagnostic bone marrow biopsy was performed). (For patients with non-malignant hematologic disorders, the primary endpoint will be rate of disease persistence at 1 year).

The goals within the complete responder arm will be slightly different than that of the non-responder arm in that in the complete responder arm we do not wish to see an elevated relapse rate increased over the currently assumed rate of 10%, while in the non-responder arm we wish to see a substantial drop in the relapse rate at 1 year, which is currently 50%.

19.1 Sample Size Determination

A maximum of 58 participants will be enrolled in this study. Accrual is expected to take 5 years. Subjects will be followed for 12 months after recruitment completion, so total study duration will be 6 years.

19.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min, and max) will be used to summarize demographic and baseline characteristics.

Additionally, descriptive statistics such as frequencies and relative frequencies will be computed for all categorical variables. Numeric variables will be summarized using simple descriptive statistics such as the mean, standard deviation and range. A variety of graphical techniques will also be used to display data, ex. histograms, boxplots, scatterplots, etc.

19.3 Primary Analysis: Efficacy

Complete Responders

In terms of the complete responders we will use two-stage design[4]3 where a true response of greater than p_0 is considered unacceptable in terms of 1 year relapse rates and evidence of such will deem the treatment not worthy of further study in this arm. The null and alternative hypotheses to be tested are H_0:$p = p_0$ versusH_1:$p > p_0$. The study design stops early for elevated relapse rates only and will proceed in two stages.

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For the complete responder strata we set the acceptable 1-year relapse rate at $p_0 = 0.10$, which leads to the following decision rule:

Stage 1: If 4 or more of the first $n_1 = 15$ evaluable patients relapse, it will be concluded that the therapy is not promising in terms of elevated relapse rates and the study will end. Otherwise, the study will progress to the second stage.

Stage 2: We will accrue 15 additional evaluable patients. If 6 or more of the total of $n_1 + n_2 = 30$ evaluable patients do relapse, it will be concluded that p is greater than p_0 and that the therapy is not promising; otherwise, it will be concluded that the therapy is worthy of further study.

The nominal significance level of this design is α=0.10. The sample size calculation is based on testing the hypotheses concerning the proportion of the population with a response to the treatment.

For the complete responder strata this two-stage design requires a potential total of $n_1 + n_2$=15+15 patients in order to achieve approximately $1-\beta$=0.80 power to detect differences of Δ=0.15 percentage points (p_0 versus$p_0 + \Delta$).

Non-Responders

For the non-responder strata we are testing H_0:$p = p_0$ versus H_1:$p < p_0$. For this test we set $p_0 = 0.50$ and our goal is to reduce the rate of 1 year relapse, which leads to the following decision rule:

Stage 1: If 7 or more of the first $n_1 = 15$ evaluable patients relapse, it will be concluded that the therapy is not promising and the study will end. Otherwise, the study will progress to the second stage.

Stage 2: We will accrue 13 additional evaluable patients. If 17 or more of the total of $n_1 + n_2 = 28$ evaluable patients do not relapse, it will be concluded that p is less than p_0 and that the therapy is efficacious; otherwise, it will be concluded that the therapy is not promising.

The nominal significance level of this design is α=0.10. The sample size calculation is based on testing the hypotheses concerning the proportion of the population with a response to the treatment.

For the non-responder strata this two-stage design requires a potential total of $n_1 + n_2$=14+14 patients in order to achieve approximately $1-\beta$=0.80 power to detect differences of Δ=0.20 percentage points (p_0 versus$p_0 - \Delta$).

19.4 Secondary Analysis

The acute and chronic GVHD rates, TRM, toxicity and overall clinical benefit rates will be computed with corresponding exact 95% confidence intervals based on the methodology of Clopper and Pearson.(74) The estimated distributions of overall and progression free survival will be obtained using the product-limit based Kaplan-Meier method. The Kaplan-Meier methodology will allow for incorporation of the censored observations thereby resulting is a more efficient estimate of the true distribution than if this information was not used. Estimates of quantities such as median duration will be obtained.

19.5 Interim Analysis and Criteria for Early Termination of the Study

Safety evaluation

For each strata if 3 or more out of the first 10 subjects have a SAE the trial will be suspended for the given strata enrollment and the treatment regimen will be re-evaluated.

19.6 Correlative Data Analysis

- Myeloid and lymphoid chimerism expressed as a percentage at the following time points: Day 30 (±10 days), Day 100 (±14 days) after stem cell infusion.
- Immune reconstitution will be evaluated by CMV dextramer analysis using flow cytometry at the following time points: baseline, Day 30 (±10 days), Day 100 (±14 days), and one year (±14 days) after stem cell infusion.

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

Data and Safety Monitoring Plan

The Principal Investigator (PI) will be responsible for continuous monitoring of the safety of the study.

Daily inpatient rounds are held on the transplant unit at which time a BMT physician reviews:

- **Medications**: Chemotherapy for conditioning regimens; prophylactic, empiric and therapeutic antimicrobials; graft-versus-host disease prophylactic and therapeutic medications and, possible drug interactions.
- **Adverse events** and/or adverse reactions to any medication, procedure, or other treatment; reports are filed according to RPCI policy and procedure.
- **Regimen-related toxicity**
- **Additional testing** or therapies such as biopsies, scans or x-rays that will direct therapeutic interventions.
- **Consent**: properly signed and dated transplant consent.
- **Patient Psychosocial Status:**
    - Compliance issues that could compromise patient safety.
    - At pretransplant, a conference is held by the BMT for all BMT patients for the purpose of describing the need for allogeneic patients to obtain lodging within a 30 mile radius of the hospital and to have a caregiver present at all times while the patient is an outpatient up to 100 days following transplant.
    - In addition, psychosocial evaluations are completed on all transplant patients by one of the BMT social workers prior to transplant, to identify any compliance issues.
- **Safety Monitoring** mandated by the BMT Standards of Care and common clinical practice. These include daily physical examinations, clinical laboratory testing, routine surveillance cultures, therapeutic drug level monitoring (i.e., Vancomycin, Tacrolimus,

Tobramycin, Cyclosporine, Sirolimus, Mycophenolate), as an inpatient. They are found in the BMT SOPs.

- Patients who have been discharged from the hospital are monitored in the BMT Clinic until all transplant-related issues are resolved and they are returned to the care of their referring physicians.
- **Performance Status**: assignment of Karnofsky Performance Status (KPS)/ Lansky Score (**Appendix A**).

In addition to weekly monitoring, the BMT **Quality Assurance** plan requires quarterly reporting to the BMT Quality Assurance Committee, which in turn reports to the RPCI Quality Assurance Committee. Indicators for BMT patient safety monitoring include:

- Patient complaints
- Reportable serious adverse events
- Variances in the delivery of standard care that do or do not result in a change in practice
- Readmissions prior to day +100 post-transplant
- Deaths occurring prior to day +100 post-transplant
- Engraftment of neutrophils and platelets

Long Term Follow-up is conducted on all transplant patients even after they have returned to the care of the referring physicians. An Annual Transplant Clinic has been established, which provides care for allogeneic patients with chronic complications, as well as assessments to identify clinical problems such as dental, bone, and psychosocial complications.

BMT Patient Outcomes are reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), and/or the National Marrow Donor Program (NMDP). Registry reports are reviewed internally prior to submission to the respective registry. These data are also entered into the RPCI BMT Database, from which patient outcomes are assessed and reviewed on an annual basis. The patients' medical records serve as original source documents for all reporting. Audits are conducted every two to three years by the CIBMTR and the NMDP.

Additionally, the RPCI Data and Safety Monitoring and Accrual Board (which reviews clinical research studies for overall study conduct, study design, rate of accrual, participant response and toxicity profile) will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMB will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

21 VULNERABLE POPULATIONS

The RPCI "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" will be followed.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not Applicable

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23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24 SETTING

Treatment will be conducted in the inpatient and outpatient setting per BMT standards of care at RPCI's BMT Center within Roswell Park Cancer Institute. For patients younger than 18 years of age or those between 18-21 years of age who are followed by the pediatric BMT physicians who attend both at RPCI as well as at Oishei Children's Hospital of Buffalo, their outpatient care will be performed mainly in the Pediatric Oncology clinic at RPCI and their inpatient BMT care will take place mainly within the BMT units at RPCI; they will have pediatric BMT attending physicians supervising their care. However, if pediatric patients require care in a pediatric intensive care unit or if they require certain procedures such as endoscopy or surgery, they will be transferred to Oishei as per BMT SOPs.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

Not Applicable

27 PRIOR APPROVALS

Not Applicable

28 COMPENSATION FOR RESEARCH-RELATED INJURY

Roswell Park Cancer Institute and Oishei Children's Hospital of Buffalo, its agents, or its employees do not compensate for or provide free care for human subjects/participants in the event that any injury results from participation in a research project. In the unlikely event that a participant/participant's child become ill or injured as a direct result of participating in this study, the participant/participant's child may receive medical care, but it is not the policy of Roswell Park Cancer Institute, Oishei Children's Hospital of Buffalo, University at Buffalo Pediatrics or the University at Buffalo, State University of New York to provide this care free even if the injury is a direct result of participation.

29 ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

30 CONSENT PROCESS

The RPCI SOP: Informed Consent Process for Research (HRP-090) will be followed.

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

The RPCI “SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)” will be followed when determining study and consent eligibility

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The RPCI “SOP: Written Documentation of Consent (HRP-091)” will be followed.

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

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32 DRUGS OR DEVICES

32.1 Fludarabine Monophosphate

32.1.1 Availability

Fludarabine monophosphate (Fludara®), a purine nucleoside analog, is commercially available as a clear, sterile solution. Each 2 milliliter vial contains 50 milligrams of fludarabine phosphate, 50 milligrams of mannitol, water for injection, and sodium hydroxide to adjust pH to 6.8. Store at 2 to 8°C (36 to 46°F).

32.1.2 Storage and Stability

Fludarabine phosphate contains no antimicrobial preservative and thus care must be taken to assure the sterility of the prepared solutions and should be discarded eight hours after initial entry.

32.1.3 Preparation

Fludarabine phosphate vials containing 50 milligrams of fludarabine phosphate, 50 milligrams of mannitol, water for injection and sodium hydroxide to adjust the pH to 6.8. The product may be further diluted for intravenous administration in 100 milliliters or 125 milliliters of 5% Dextrose for Injection USP or 0.9% Sodium Chloride, USP.

32.1.4 Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Fludarabine will be delivered as a piggy-bag via an ongoing IV line, over a period of 30 minutes.

32.2 Cyclophosphamide

32.2.1 Availability

Cyclophosphamide (Cytoxan®), an alkylating agent for injection, is commercially available as a powder for injection in 500 milligram, 1 gram, and 2 gram vials.

32.2.2 Storage and Stability

Intact vials should be stored at or below 25°C (77°F). Following reconstitution with sterile diluent, cyclophosphamide is stable for up to 24 hours at room temperature and for up to 36 hours if refrigerated.

32.2.3 Preparation

Reconstitute Cyclophosphamide using 0.9% Sodium Chloride Injection, USP or Sterile Water for Injection, USP, with 25 mL for a 500 mg vial, 50 mL for a 1 g vial, and 100 mL for a 2 g vial, for a total concentration of 20 mg/mL.

32.2.4 Administration

Cyclophosphamide to be administered IV over 2 hours.

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32.3 Sirolimus

32.3.1 Availability

Sirolimus is an agent that inhibits the activation of the mammalian Target of Rapamycin (mTOR). It is available for administration as an oral solution containing 1 mg/mL of sirolimus or as a white, triangular-shaped tablet containing 1 mg of sirolimus, or as a yellow triangular-shaped tablet containing 2 mg of sirolimus. Sirolimus is rapidly absorbed. The systemic availability of sirolimus is 14% after administration of the solution and 27% after administration of tablets. Sirolimus is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver. The majority of sirolimus is ultimately excreted into the stool, with a small amount excreted in the urine. Due to the reduced intensity nature of the conditioning regimen, an oral regimen should be tolerated.

32.3.2 Storage and Stability

Sirolimus solution should be stored, protected from light, and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., not more than 15 days for the bottles). A dose of sirolimus solution may be kept in an oral syringe at room temperature for up to 24 hours. Sirolimus tablets should be stored at 20°C to 25°C (USP Controlled Room Temperature) (68° to 77°F). Use cartons to protect blister cards and strips from light.

32.3.3 Preparation

For Oral Use

For sirolimus solution, a syringe and cap are provided for dosing and the product may be kept in the syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution, the preparation should be used immediately.

Sirolimus solution provided in bottles may develop a slight haze when refrigerated. If such a haze occurs allow the product to stand at room temperature and shake gently until the haze disappears. The presence of this haze does not affect the quality of the product.

Sirolimus tablets should be dispensed in a tight, light-resistant container.

32.3.4 Administration

Oral therapy should be started on Day +5, at a dose of 1 mg daily, with dose adjustments to keep the trough between 5-10 ng/mL. Either sirolimus solution or tablets may be utilized, as per discretion of the treating physician. Co-administration with azole anti-fungal therapy will be avoided whenever possible in order to mitigate the risk of drug-drug interactions (for example, if posaconazole is given between 6 – 8 AM then sirolimus will be given between 1 - 3 PM).

32.4 Mycophenolate

32.4.1 Availability

Mycophenolate (CellCept®), a 2-morpholinoethyl ester of mycophenolic acid (MPA), inosine monophosphate dehydrogenase (IMPDH) inhibitor, is available for oral administration as capsules

containing 250 milligrams of mycophenolate mofetil, tablets containing 500 milligrams of mycophenolate mofetil, and as a powder for oral suspension, which when constituted contains 200 milligrams/milliliter mycophenolate mofetil.

Each vial of mycophenolate intravenous contains the equivalent of 500 milligrams mycophenolate mofetil as the hydrochloride salt. Reconstitution and dilution with 5% Dextrose Injection USP yields a solution of mycophenolate mofetil, 6 milligrams/milliliter.

32.4.2 Storage and Stability

The mycophenolate mofetil powder for reconstitution and reconstituted solution should be stored at 25°C (77°F); however, temperature excursions between 15°C to 30°C (59°F to 86°F) are permitted.

32.4.3 Preparation and Administration

Mycophenolate mofetil hydrochloride for injection (CellCept Intravenous) must be reconstituted and diluted to a concentration of 6 mg/mL using 5% Dextrose Injection USP. CellCept Intravenous is incompatible with other intravenous infusion solutions. Following reconstitution, CellCept Intravenous must be administered by slow intravenous infusion over a period of NO LESS THAN 2 HOURS by either peripheral or central vein.

CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION

Refer to package insert for detailed instructions.

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34 APPENDICES/ SUPPLEMENTS

Appendix A Karnofsky/ Lansky Scale

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age ≥ 1 year and <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	**100**	Fully active
90	Able to carry on normal activity	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	**60**	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	**40**	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	**20**	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	**10**	Completely disabled, not even passive play

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Appendix B ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA

Participant Name:_____

Medical Record No.: _____

Title: A Phase II Trial of Haploidentical Allogeneic Stem Cell Transplantation Utilizing Mobilized Peripheral Blood Stem Cells.

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Any disease that is considered transplant eligible per TCT standards.	
☐	☐	☐	2. Disease response noted (i.e. CR, non-CR, or not applicable): Assessed as per disease specific criteria (see Section 3.5).	
☐	☐	☐	3. Suitable related haploidentical donor identified per transplant service: Recipient should not have HLA antibodies to potential donor. If the recipient does have HLA antibodies to the potential donor, an alternative donor is preferred. However, if there are no suitable alternative donors, the anti-HLA antibodies should be depleted per transplant service guidelines. • Haploidentical donors that are ABO compatible with the recipient are preferred. Minor ABO incompatibility is preferred to major ABO incompatibility. Major ABO incompatibility between recipient and donor is the least preferred but still acceptable for this study. • It is preferred that the haploidentical donor must be available to donate on day -1 and day 0 at RPCI, so that fresh product can be processed by the RPCI Stem Cell Lab and administered to the patient on day 0. While less preferable, cryopreserved product may be utilized on this protocol.	
☐	☐	☐	4. Age ≥ 4 (age ≥ 1 once Oishei Children's Hospital BMT unit is open) and ≤ 80 years.	
☐	☐	☐	5. Have the following clinical laboratory values: • Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) > 40% predicted, corrected for hemoglobin and/or alveolar ventilation. • Cardiac: left ventricular ejection fraction > 40%. • Bilirubin, liver alkaline phosphatase, SGOT or SGPT ≤ 3 x upper limit of normal. • Calculated creatinine clearance> 40 cc/min by the modified Cockroft-Gault formula for adults or the Schwartz formula for pediatrics (refer to Appendix I).	
☐	☐	☐	6. Have a Karnofsky (adult) or Lansky (for ≤16 years) performance status ≥ 60% (refer to Appendix A).	
☐	☐	☐	7. Patient must be able to pass Radiation evaluation (i.e.: able to receive 200 cGy).	

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INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	8. Patients who have failed a prior autologous transplant are eligible; however, at least 90 days must have elapsed between the start of this reduced intensity conditioning regimen and the last transplant if patient had a prior autologous BMT.	
☐	☐	☐	9. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	10. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	
☐	☐	☐	11. If patient is planned to use a fully matched donor, patient is excluded from trial; patient must be planned to undergo a haploidentical matched transplant to participate on study. Patient is still eligible for trial regardless of donor options if PI feels that haplo transplant is in the patient's best interest per clinical decision.	

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

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Appendix C ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: A Phase II Trial of Haploidentical Allogeneic Stem Cell Transplantation Utilizing Mobilized Peripheral Blood Stem Cells.

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Participants who have had chemotherapy (not including molecularly targeted agents; examples include, but are not limited to, tyrosine kinase inhibitors such as FLT3 inhibitors and IDH2 inhibitors), radiation treatment and/or surgery 7 days prior starting conditioning regimen. Those who have not recovered sufficiently from adverse events due to agents administered more than 2 weeks earlier are also ineligible. Exceptions may be made on a case-by-case basis after discussion with the PI.	
☐	☐	☐	2. Uncontrolled CNS disease (for hematologic malignancies) per PI discretion.	
☐	☐	☐	3. Child-Pugh class B and C liver failure (refer to Appendix J).	
☐	☐	☐	4. Concomitant active malignancy that would be expected to require chemotherapy within 3 years of transplant (other than non-melanoma skin cancer). Exception would include any concurrently existing malignancy that could be treated with a transplant per PI discretion. (Example: Patient has AML but a history of mastocytosis.)	
☐	☐	☐	5. Uncontrolled diabetes mellitus, cardiovascular disease, active serious infection or other condition which, in the opinion of treating physician, would make this protocol unreasonably hazardous for the patient.	
☐	☐	☐	6. Known HIV positive.	
☐	☐	☐	7. Pregnant or nursing female participants.	
☐	☐	☐	8. Patients who in the opinion of the treating physician are unlikely to comply with the restrictions of allogeneic stem cell transplantation based on formal psychosocial screening.	
☐	☐	☐	9. Patients with donor specific HLA antibodies with a titer greater than 3000 MFI (whether or not they have undergone a desensitization protocol).	
☐	☐	☐	10. Patients who have undergone a prior allogeneic hematopoietic or (other organ) transplant.	
☐	☐	☐	11. Treating physician considers the potential HLA haploidentical donor to be ineligible to receive G-CSF, and/or concern on the part of the treating physician for risk of harm to the potential donor with administration of G-CSF, and/or refusal by the potential donor (or donor's guardian) to receive G-CSF.	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	12. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	
☐	☐	☐	13. Received an investigational agent within 14 days prior to enrollment. Exceptions made be made on a case-by-case basis after discussion with PI.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

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Appendix D Donor Eligibility Criteria

- Haploidentical Related Donor: Matched at a minimum of 6 to a maximum of 8 of 12 HLA loci: A, B, C, DRB1, DQ and DP.
- Donor must be healthy and have nonreactive test results for all infectious disease assays as required by state and federal regulations. Donors who screen seropositive for hepatitis and/or syphilis must be cleared by infectious disease consultation.
- The donor must have no uncontrolled cardiopulmonary, renal, endocrine, hepatic or psychiatric disease to render donation unsafe.
- The donor (or parent if minor) must give informed consent for peripheral blood stem cell collection.
- Donors who have poor peripheral venous access, may require central venous line placement for stem cell apheresis.
- Pediatric relatives of the patient (< 18 years of age) who are at least 2.5 years of age, and who have been medically cleared for peripheral blood stem cell mobilization and collection by a pediatric hematologist/oncologist who is not primarily responsible for the oncologic care of the intended related recipient, are eligible to donate PBSCs on this trial.
- In the case of a potential pediatric donor (< 18 years of age), as recommended by the Worldwide Network for Blood and Marrow Transplantation(75), donor evaluation and medical clearance for PBSC mobilization and collection must be performed by a pediatric hematologist (or pediatric oncologist) who is not the primary hematologist/oncologist for the patient (the potential recipient). If the physician who is evaluating the potential pediatric donor does not feel that it is safe for the potential donor to undergo PBSC mobilization and collection, or that it is otherwise not in the best interest of the potential donor to do so (an ethics consultation may be utilized as per the evaluating physician's discretion), then the potential donor will not undergo PBSC mobilization and collection. If another suitable haploidentical donor cannot be found for the patient, then the patient will be ineligible for this study. PBSC collection on pediatric donors will be performed as per BMT SOPs. Given that the use of G-CSF has not been studied in donors younger than 2.5 years of age but data demonstrating safety of G-CSF in donors 2.5 years of age and older is available(76), donors must be at least 2.5 years of age at the time of PBSC mobilization for this study.
- PBSC donation is not allowed from individuals who are less than 30 months of age on this trial.
- Pregnant women are not eligible to be donors on this study.

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Allogeneic Hematopoietic Cell Verification Form:
Donor Acceptance Criteria

Donor Name: _____

Medical Record No.: _____

Title: A Phase II Trial of Haploidentical Allogeneic Stem Cell Transplantation Utilizing Mobilized Peripheral Blood Stem Cells.

ACCEPTANCE CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for an acceptable donation.**	**Date**
☐	☐	☐	1. Haploidentical related donor identified.	
☐	☐	☐	2. Documented verification of healthy donor with nonreactive test results for all infectious disease assays as required by state and federal regulations (Donors who screen seropositive for hepatitis and/or syphilis must be cleared by infectious disease consultation).	
☐	☐	☐	3. Donor has no documented uncontrolled cardiopulmonary, renal, endocrine, hepatic or psychiatric disease to render donation unsafe.	
☐	☐	☐	4. Donor (or parent if minor) has given informed consent for peripheral blood stem cell collection.	
☐	☐	☐	5. Criteria for donation as per BMT SOPs are fulfilled.	

Donor/donation meets all acceptance criteria: ☐ **Yes** ☐ **No**

If "NO", donation cannot be used for this study.

Investigator (or designee) Signature: _____ **Date:** _____

Printed Name of Investigator (or designee): _____

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Appendix E Stem Cell Infusion

Day 0 is the day on which the stem cells are infused. The procedure of infusing stem cell products may be performed under the supervision of the attending physician.

- See BMT form 519-F-626 for standard ordering process, and Stem Cell Lab Policies as per SOPs)
- Stem cells are to remain sterile throughout the infusion process.
- All patients require continuous pulse oximetry monitoring during the procedure, with oxygen equipment available in the patient's room.
- All patients will have vital signs recorded before the procedure and at timed intervals during and after stem cell infusion.
- Emergency drugs, such as Benadryl, epinephrine and corticosteroids will be available for use in appropriate doses. As noted below, corticosteroids should be avoided if possible.
- No other blood products should be given on the day of transplant, especially within 8 hours of planned infusion time.
- Stem cells must be infused without the use of a blood filter through a wide lumen central catheter.
- The minimum PBSC dose is 5 x 10^6 CD34+ cells/kg of recipient weight; the maximum PBSC dose is 30 x 10^6 CD34+ cells/kg of recipient weight.
- No more than 480 ml of stem cells may be infused at one time and the transplant may need to be split into a morning and afternoon infusion at the discretion of the attending physician.
- Patients will be pre-medicated according to RPCI SOP Stem Cell reinfusion (see 511 F-422 Physician Order Form) however hydrocortisone and all glucocorticoids will be avoided if considered safe to do so by the treating clinician.

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Appendix F Schedule of Research-Related Procedures and Observations

Tests/Observations	Pre-Rx (Screening/ Baseline) [1]	Day 0[2]	Post-Rx[3]
HCT-CI/Age composite score	X		
Karnofsky/Lansky Performance	X		X[4]
Temperature	X		X Starting on Day +1 through + 10 (including Day +1 and Day +10)
Hematology (CBC/ Diff)	X		
Chemistry (CMP) with LDH	X		
Serology (HIV, Hepatitis[5], CMV)	X		
Quantitative Immunoglobulins	X		X[6]
Urinalysis biochemical	X		As clinically indicated
HLA typing	X		
Creatinine Clearance	X		
PFT's including DLCO	X		Day 100, Day 365 [±14 days], then as clinically indicated
PET scan (for patients with myeloma)	X		
MUGA or ECHO	X		
EKG	X		
BM aspirate, biopsy[7]	X		Day 30 (±10 days) , Day 100 (±14 days), and 1 year (±14 days)[8] (refer to Section 11.7.1)
Chest X-ray (PA and lateral)	X		
Disease Evaluation: Assessment of Response, to include CT Scan and/or PET as clinically appropriate[9]	X		X
Peripheral blood for chimerism			Day 30 (±10 days) , Day 100 (±14 days), at 1 year (±14 days), then as indicated (refer to Section 11.7.1)
Peripheral blood for flow	X		Day 30 (±10 days) , Day 100 (±14 days) at 1 year (±14 days), then as indicated (refer to Section 11.7.2)
Stem Cell Infusion		X	
Adverse events[10]	X	X	X[11]

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1 Pre-Rx testing is to be obtained **within 60 days of enrollment** unless otherwise noted.
2 Day 0: Date/Day of stem cell infusion.
3 All testing will be performed post-Rx as clinically indicated. Only mandatory tests are included in this table.
4 Weekly after discharge until Day 100 after stem cell infusion.
5 Hep B virus surface, Ag; Hep B virus core antibody, total; Hep C virus, antibody; only if clinically indicated: HCV RNA, HBV DNA
6 Post-transplant SPEP, IFE, Quantitative immunoglobulins, serum beta-2 microglobulin, kappa/lambda free light chains and 24 hour urine for protein electrophoresis and free light chains will be done only for patients with multiple myeloma on Day 100-160 and then as clinically indicated.
7 BM aspirate and biopsy will be performed for patients with leukemias and bone marrow failure states only. Patients with other malignancies will have BM aspirate and biopsy only if bone marrow was involved previously.
8 If the patient is medically unfit or has scheduling difficulty, delay is allowed at all follow-up time points.
9 Patients with non-Hodgkin's and Hodgkin's lymphoma only: Baseline, Day 100 (± 14 days) post stem cell infusion and one year (± 14 days) post stem cell infusion. ***All other patients***: as clinically indicated. Restaging workup for assessment of disease response per Appendix M and Appendix N.
10 Serious Adverse Events from Day -6 until Day +30 will be reported to Clinical Research Services.
11 Post-infusion assessments:

- Acute GVHD: weekly for the first 100 days post-transplant, every 3 weeks (±7 days) from Day 100 through Day 180, and monthly (±14 days) through Day 365 post-transplant.
- Chronic GVHD: weekly for the first 100 days post-transplant, every 3 weeks (± 7 days) from Day 100 through Day 180, and monthly (± 14 days) through Day 365 post-transplant.

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Appendix G Criteria for Acute Graft-vs-Host Disease

Clinical staging of acute graft-vs.-host disease according to organ involvement

STAGE	SKIN	LIVER	LOWER INTESTINAL TRACT	UPPER INTESTINAL TRACT
0	No rash	Bilirubin < 2.0 mg/dL < 34 µmol/L	Diarrhea < 500 ml/day Peds: < 10 ml/kg/day	No persistent anorexia, nausea, or vomiting
+	Maculopapular rash < 25% of body surface	Bilirubin 2.0-3.0 mg/dL 34-52 µmol/L	Diarrhea 500-1000 ml/day Peds: 10-19.9 ml/kg/day	Persistent anorexia, nausea, or vomiting
++	Maculopapular rash 25-50% of body surface	Bilirubin 3.1-6.0 mg/dL 53-103 µmol/L	Diarrhea > 1000-1500 ml/day Peds: 20-30 ml/kg/day	
+++	> 50% body surface	Bilirubin 6.1-15.0 mg/dL 104-256 µmol/L	Diarrhea > 1500 ml/day Peds: > 30 ml/kg/day	
++++	Generalized erythroderma with bullous formation and/or desquamation	Bilirubin > 15.0 mg/dL > 256 µmol/L	Severe abdominal pain with or without ileus	

(https://www.cibmtr.org/DataManagement/DataCollectionForms/Documents/2450/Rev4.0/2450R4.0.pdf)

Glucksberg et al. Transplantation 1974;18:295-304
Thomas et al. New Engl J Med 1975;292:895-902
Przepiorka et al. Bone Marrow Transplant 1995;15:825-828

Clinical (Glucksberg) grading of severity of acute graft-vs-host disease

GRADE	DEGREE OF ORGAN INVOLVEMENT
I	+ to ++skin rash; no gut involvement; no liver involvement; no decrease in clinical performance

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II	+ to +++ skin rash; + gut involvement or + liver involvement (or both); mild decrease in clinical performance
III	++ to +++ skin rash; ++ to +++ gut involvement or ++ to ++++ liver involvement (or both) marked decrease in clinical performance
IV	Similar to Grade II with ++ to ++++ organ involvement and extreme decrease in clinical performance

Source: Thomas et al, N Engl. J Med. 1975; 292, 832

IBMTR Severity Index

A – Stage 1 skin involvement, no liver or gut involvement
B – Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement
C – Stage 3 skin, liver, or gut involvement
D – Stage 4 skin, liver or gut involvement

Source: Rowlings et al., Br J Haematol 1997; 97:855

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Appendix H Clinical Grading of Chronic GVHD

Involvement	Description
Limited	Localized skin involvement and/or hepatic dysfunction due to chronic GVHD.
Extensive	One or more of the following: 1) Generalized skin involvement; or 2) Liver histology showing chronic aggressive hepatitis, bridging necrosis or cirrhosis, or 3) Involvement of the eye, or 4) Involvement of minor salivary glands or oral mucosa, or 5) Involvement of any other target organ (lung, GI, GU, musculoskeletal, serositis, etc…).
Severity	**Description**
Mild	Signs and symptoms of chronic GVHD do not interfere substantially with function and do not progress once appropriately treated with local therapy or standard systemic therapy (i.e., corticosteroids and/or CSA/Tacro).
Moderate	Signs and symptoms of chronic GVHD interfere somewhat with function despite appropriate therapy or are progressive through first line systemic therapy (i.e., corticosteroids and/or CSA/Tacro).
Severe	Signs and symptoms of chronic GVHD limit function substantially despite appropriate therapy or are progressive through second line therapy.

*Modified from CIBMTR Form 2100, revision 4 (.Center for International Blood & Marrow Transplant Research: Post-HCT Follow-Up Data. (77)

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Appendix I Creatinine Clearance

COCKROFT GAULT FORMULA (MODIFIED FOR BSA) FOR ESTIMATION OF CREATININE CLEARANCE ABOVE AGE 18*

CLEARANCE (ml/min)

Male = (140-age) x IBW (kg) / 72 x SrCr

Female= male clearance x 0.85

IBW (male) = 50 + 0.91(Height (cm) - 152)

IBW (female) = 45 + 0.91(Height (cm) - 152)

SrCr in mg/dL

SCHWARTZ FORMULA FOR ESTIMATION OF CREATININE CLEARANCE UP TO AGE 18*

CLEARANCE (ml/min/1.73 m^2) = K x L / SrCr

K = age adjusted constant, L = length in centimeters, SrCr in mg/dL.

Age	K
Children 1-13 years old	0.55
Adolescent females 13-18 years old	0.55
Adolescent males 13-18 years old	0.70

Based on: Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259-263, 1976.

*Can use either serum or plasm a creatinine levels

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Appendix J Child-Pugh Classification of Liver Failure

Measurement	Points Scored		
	1	2	3
Encephalopathy	None	1 and 2	3 and 4
Ascites	None	Slight	Moderate
Bilirubin (mg/100 mL)	1.0 – 2.0	2.0 – 3.0	> 3.0
Albumin (gm/100 mL)	3.5	2.8 - 3.5	< 2.8
Prothrombin time (sec. prolonged)	1 - 4	4 - 6	>6
For PBC, bilirubin (mg/100 mL)	1 - 4	4 - 10	>10

Child - Pugh Classification:

A = 1 – 6

B = 7 – 9

C = 10-15

Appendix K AML – Prognostic Groups(78)

Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

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Appendix L Arm Distribution Criteria (79)

Acute Myeloid Leukemia

Complete Remission (CR)

Hematologic complete remission is defined as meeting all of the following response criteria:

- < 5% blasts in the bone marrow
- Evidence of trilineage hematopoiesis in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Neutrophils ≥ 1,000/μL
- Platelets ≥ 100,000/μL
- Transfusion independent

Complete Remission with Incomplete Hematologic Recovery (CRi)

Hematologic complete remission with incomplete hematologic recovery is defined as meeting all of the following response criteria:

- < 5% blasts in the bone marrow
- Evidence of trilineage hematopoiesis in the bone marrow
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)

Acute Lymphoblastic Leukemia

Complete Remission (CR)

Hematologic complete remission is defined as meeting **all** of the following response criteria:

- < 5% blasts in the bone marrow
- Evidence of trilineage hematopoiesis in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- ANC (absolute neutrophil count) ≥ 1,000/μL
- Platelets ≥ 100,000/μL

Complete Remission with Incomplete Hematologic Recovery (CRi)

Hematologic complete remission with incomplete hematologic recovery is defined as meeting all of the following response criteria:

- < 5% blasts in the bone marrow
- Evidence of trilineage hematopoiesis in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)

Multiple Myeloma* / Plasma Cell Disorder

Stringent Complete Remission (sCR)

Follows criteria for CR as defined below, **plus all of the following**:

- Normal free light chain ratio
- Absence of clonal cells in the bone marrow by immunohistochemistry, immunofluorescence, flow cytometry (MRD testing)

Complete Remission (CR)

A treatment response where all of the following criteria are met:

- Negative immunoelectrophoresis (immunofixation) on serum and urine samples
- Disappearance of any soft tissue plasmacytomas
- < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)
- No known evidence of new or progressive bone lesions on radiographic studies.

For recipients with **non-secretory myeloma**, all of the following criteria must be met:

- Disappearance of all soft tissue plasmacytomas
- < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)
- No known evidence of new or progressive bone lesions on radiographic studies.

Very Good Partial Response (VGPR)

- Absence of soft tissue plasmacytoma

One or more of the following must be present:

- ≥ 90% reduction in serum M-protein and urine M-protein level < 100 mg/24 hours

OR

- Serum and urine M-protein detectable by immunofixation but not on electrophoresis

At diagnosis, if:

- M protein is < 1 g/dL, you must use serum free light chain or urine measurement
- IgA monoclonal protein, you must use an estimate by total IgA or HevyLite®
- Urine M-protein is < 200 mg/24 hours, use serum free light chains or if serum free light chains are not elevated, then use nonsecretory myeloma criteria

*Modified based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma(80)

Hodgkin and Non-Hodgkin Lymphoma

Complete Remission (CR)

- Complete disappearance of all known disease. For typically PET-avid lymphoma, a post-treatment residual mass of any size is permitted as long as it is PET negative. For variably, PET-avid lymphoma, all lymph nodes and nodal masses must have regressed as measured by CT to < 1.5 cm (for nodes > 1.5 cm before therapy) or < 1 cm (for nodes 1.1 cm to 1.5 cm before therapy)

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CRu

- All CR criteria are met except, there may be CT scan abnormalities of uncertain significance. PET scan must be negative.

Chronic Lymphocytic Leukemia

Complete Response (CR)

All of the following:

- Any lymphadenopathy must be ≤ 1.5 cm in the widest dimension
- If present, splenomegaly must be < 20 cm in the widest dimension on radiographic imaging
- Neutrophils ≥ 1.5×10^9/L
- Platelets > 100×10^9/L
- Hemoglobin > 11 g/dL
- Lymphocytes < 4×10^9/L
- Bone marrow < 30% lymphocytes
- Absence of constitutional symptoms (including weight loss, fever, and night sweats)

CRi

All of the following:

- No evidence of lymphadenopathy
- No organomegaly

Absence of constitutional symptoms (including weight loss, fever, and night sweats)

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Appendix M Post-Transplant Response Criteria (79)

Acute Myeloid Leukemia

Continued Complete Remission (CCR)

- For patients transplanted in CR, the best response post BMT is CCR as long as there is no documented disease progression

Complete Remission (CR)

Hematologic complete remission is defined as meeting all of the following response criteria for at least four weeks.

- < 5% blasts in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)

Relapse (REL)

Relapse is defined as the recurrence of disease after CR, meeting one or more of the following criteria:

- ≥ 5% blasts in the marrow or peripheral blood
- New or recurrence of extramedullary disease

Acute Lymphoblastic Leukemia

Continued Complete Remission (CCR)

- For patients transplanted in CR, the best response post BMT is CCR as long as there is no documented disease progression

Complete Remission (CR)

Hematologic complete remission is defined as meeting all of the following response criteria for at least four weeks.

- < 5% blasts in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)

Relapse (REL)

Relapse is defined as the recurrence of disease after CR, meeting one or more of the following criteria:

- ≥ 5% blasts in the marrow or peripheral blood
- New or recurrence of extramedullary disease

Myelodysplastic Syndrome (MDS)

Continued Complete Remission (CCR)

- For patients transplanted in CR, the best response post BMT is CCR as long as there is no documented disease progression

Complete Remission (CR)

Bone marrow evaluation:

- < 5% myeloblasts with normal maturation of all cell lines

Peripheral blood evaluation:

- Hemoglobin ≥ 11 g/dL un-transfused within 7 days without erythropoietic support
- ANC ≥ 1000/mm^3 without myeloid growth factor support
- Platelets ≥ 100,000/mm^3 without thrombopoietic support
- 0% blasts in blood

Hematologic Improvement (HI)

- <5% blasts in the bone marrow

Hematologic improvement – erythropoietic (HI-E)

- Hemoglobin increase of ≥ 1.5 g/dL un-transfused for 7 days

Hematologic improvement – platelets (HI-P)

- For pre-treatment platelet count of > 20 ×10^9, platelet absolute increase of ≥ 30 ×10^9
- For pre-treatment platelet count of < 20 ×10^9, platelet absolute increase of ≥ 20 ×10^9 and ≥ 100% increase from pre-treatment level

Hematologic improvement – neutrophils (HI-N)

- Neutrophil count increase of ≥ 100% from pre-transplant level and an absolute increase of ≥ 500/mm^3

No Response (NR)/Stable Disease (SD)

- Does not meet the criteria for at least HI; but no evidence of disease progression to AML.

Relapse/Progression from Complete Remission (Rel from CR or HI)

Requires at least one of the following:

- Bone marrow blasts >5% and clonal
- At least a 50% decrease in platelets or granulocytes that is related to the malignant clonal population of cells (not due to ABO incompatibility, medication, angiopathy, or other nonmalignant causes)
- The hemoglobin level must decrease by at least 1.5 g/dL from pre-transplant level.

Progression to AML

- ≥ 20% blasts in the blood or bone marrow

Multiple Myeloma / Plasma Cell Disorder (Including WM)

Continued Complete Remission (CCR)

- For patients transplanted in CR, the best response post BMT is CCR as long as there is no documented disease progression

Stringent Complete Remission (sCR)

Follows criteria for CR as defined below, plus all of the following:

- Normal free light chain ratio
- Absence of clonal cells in the bone marrow by immunohistochemistry, immunofluorescence, flow cytometry (MRD testing)

Complete Remission (CR)

- A treatment response where all of the following criteria are met:
- Negative immunoelectrophoresis (immunofixation) on serum and urine samples
- Disappearance of any soft tissue plasmacytomas
- < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)
- No known evidence of new or progressive bone lesions on radiographic studies.

For recipients with non-secretory myeloma, all of the following criteria must be met:

- Disappearance of all soft tissue plasmacytomas
- < 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)
- No known evidence of new or progressive bone lesions on radiographic studies.

Very Good Partial Response (VGPR)

- Absence of soft tissue plasmacytoma

One or more of the following must be present:

- ≥ 90% reduction in serum M-protein and urine M-protein level < 100 mg/24 hours

OR

- Serum and urine M-protein detectable by immunofixation but not on electrophoresis

At diagnosis, if:

- M protein is < 1 g/dL, you must use serum free light chain or urine measurement)
- IgA monoclonal protein, you must use an estimate by total IgA or HevyLite®
- Urine M-protein is < 200 mg/24 hours, use serum free light chains or if serum free light chains are not elevated, then use nonsecretory myeloma criteria

Partial Response (PR)

Both of the following must be present:

- ≥ 50% reduction in serum M-protein
- Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours.

At diagnosis, if:

- M protein is < 1 g/dL, you must use serum free light chain or urine measurement)
- IgA monoclonal protein, you must use an estimate by total IgA or HevyLite®
- Urine M-protein is < 200 mg/24 hours, use serum free light chains or if serum free light chains are not elevated, then use nonsecretory myeloma criteria

In addition to the above-listed criteria, if soft tissue plasmacytomas were present at baseline, a ≥ 50% reduction in their size is also required.

Stable Disease (SD)

- Does not meet the criteria for CR, VGPR, PR, or PD.

Progressive Disease (PD)

Requires **one or more** of the following:

- Increase of ≥ 25% from the lowest post-transplant response value achieved in:
- Serum M-component with an absolute increase ≥ 0.5 g/dL
- Urine M-component with an absolute increase ≥ 200 mg/24 hours;
- For recipients without measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL;
- Bone marrow plasma cell percentage with absolute percentage increase of ≥ 10%;
- Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas

Chronic Myeloid Leukemia

Continued Complete Remission (CCR)

- For patients transplanted in CR, the best response post BMT is CCR as long as there is no documented disease progression

Complete Hematologic Remission (CR)

A treatment response where all of the following criteria are met:

- White blood count is < 10×10^9/L, without immature granulocytes and with < 5% basophils
- Platelet count < 450×10^9/L
- Non-palpable spleen

Complete Molecular Remission (81)

- 0% BCR/ABL transcripts detected in peripheral blood or bone marrow

Major Molecular Remission

- >0-0.1% BCR/ABL transcripts detected in peripheral blood or bone marrow

Complete Cytogenetic Response

- 0% Ph+ cells detected in bone marrow

Partial Cytogenetic Response

- >0-35% Ph+ cells in bone marrow

Minor Cytogenetic Response

- >35-65% Ph+ cells in bone marrow

Minimal Cytogenetic Response

- >65-95% Ph+ cells in bone marrow

No Cytogenetic Response

- >95% Ph+ cells in bone marrow

Chronic Phase

- Characterized by relatively few blasts (<10%) present in the blood and bone marrow. Symptoms are often not present. The chronic phase may last several months to years, depending on the recipient and the treatment they receive.

Accelerated Phase

One or more of the following must be present:

- 10%-19% blasts in blood or marrow
- ≥ 20% basophils in peripheral blood
- Clonal marrow cytogenetic abnormalities in addition to the single Philadelphia chromosome (clonal evolution)
- Increasing spleen size, unresponsive to therapy
- Increasing WBC, unresponsive to therapy
- Thrombocytopenia (platelets < 100,000), unrelated to therapy
- Thrombocytosis (platelets > 1,000,000), unresponsive to therapy

Blast Phase

Characterized by having ≥ 20% blasts (formerly ≥ 30%) in the peripheral blood or bone marrow. Having extramedullary blastic infiltrates (i.e., myeloid sarcoma, granulocytic sarcoma, or chloroma) also qualifies as blast phase. The red cell, platelet, and neutrophil counts may decrease and episodes of infection and bleeding may result. Symptoms such as fatigue, shortness of breath, abdominal pain, bone pain, and spleen enlargement may occur.

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Relapse

For reporting purposes, relapse is defined as recurrence of disease after complete hematologic remission. In general, relapse should be confirmed by a clinical / hematologic assessment (e.g., pathology, CBC, or clinical exam).

Progression

For reporting purposes, progression is defined as any of the following changes in disease status:

- Advancement from chronic phase to accelerated phase.
- Advancement from chronic phase to blast phase.
- Advancement from accelerated phase to blast phase.

Hodgkin and Non-Hodgkin Lymphoma

Continued Complete Remission (CCR)

- For patients transplanted in CR, the best response post BMT is CCR as long as there is no documented disease progression

Complete Remission (CR)

Complete disappearance of all known disease. For typically PET-avid lymphoma, a post-treatment residual mass of any size is permitted as long as it is PET negative. For variably PET-avid lymphoma, all lymph nodes and nodal masses must have regressed as measured by CT to ≤ 1.5 cm (for nodes > 1.5 cm before therapy) in the longest diameter or ≤ 1 cm (for nodes 1.1 cm to 1.5 cm before therapy).

Bone Marrow (optional as part of work-up unless it was positive for disease immediately prior to transplant): If bone marrow was positive any time prior to transplant, it must be repeated and negative to confirm CR.

Partial Remission (PR)

- ≥ 50% reductions in the greatest diameter of up to six of the largest dominant nodes or nodal masses, extranodal sites and no new sites of lymphoma

Stable Disease

- Does not meet criteria for CR, PR, or PD

Progressive Disease

- Any new lesion and/or > 50% increase in the least diameter of previously involved sites
- New or recurrent involvement of bone marrow
- New or recurrent extranodal disease

Chronic Lymphocytic Leukemia

Continued Complete Remission (CCR)

- For patients transplanted in CR, the best response post BMT is CCR as long as there is no documented disease progression

Complete Response (CR)

All of the following:

- Any lymphadenopathy must be ≤ 1.5 cm in the widest dimension
- If present, splenomegaly must be < 20 cm in the widest dimension on radiographic imaging
- Neutrophils ≥ 1.5×10^9/L
- Platelets > 100×10^9/L
- Hemoglobin > 11 g/dL
- Lymphocytes < 4×10^9/L
- Bone marrow < 30% lymphocytes
- Absence of constitutional symptoms (including weight loss, fever, and night sweats)

Partial Response (PR)

- ≥ 50% decrease in peripheral blood lymphocyte count from pretreatment value
- ≥ 50% reduction in lymphadenopathy if present pretreatment
- ≥ 50% reduction in liver and/or spleen size if enlarged pretreatment

One or more of the following:

- Neutrophils ≥ 1.5 ×109/L or 50% improvement over baseline
- Platelets > 100 ×109/L or 50% improvement over baseline
- Hemoglobin > 11 g/dL or 50% improvement over baseline

Stable Disease (SD)

Not meeting the definition of complete response, partial response, or progressive disease.

Progressive Disease (PROG)/Relapse

One or more of the following:

- ≥ 50% increase in the sum of the products of ≥ 2 lymph nodes (≥ 1 lymph node must be ≥ 2 cm) or new nodes
- ≥ 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly
- ≥ 50% increase in absolute lymphocyte count to ≥ 5 ×109/L
- Transformation to a more aggressive histology

Bone Marrow Failure Disorders, including Aplastic Anemia

Complete Response:

- At least 20% cellularity in the bone marrow with neutrophil and platelet engraftment (ANC >500 and Platelets >20)

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No Response:

- Does not meet definition of CR

Other Non-Malignant Hematologic Disorders, Immune Disorders

Complete Response:

- Disappearance of signs/symptoms and absence of evidence of the presence of the underlying disease

No Response:

- Persistence of the underlying disease

Appendix N Myelofibrosis, Polycythemia Vera, and CMML Post-Transplant Response Criteria

Myelofibrosis (82)

CCR: For those patients in CR at baseline, continued CR.

Complete remission (CR)	All of the following criteria should be met: • Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly • Peripheral blood count remission (hemoglobin ≥ 11 g/dL, platelets ≥ 100 x10^9/L, neutrophils ≥ 1.0 x10^9/L), all 3 blood counts should also be no higher than upper limit of normal • Normal white cell differential including absence of nucleated red cells, blasts, and immature myeloid cells on the blood film, in the absence of splenectomy (1) • Histologic remission on bone marrow trephine: normocellular for age, ≤ 5% myeloblasts, and osteomyelofibrosis grade ≤ 1 (2)
Partial remission (PR)	All CR criteria met except bone marrow histologic remission
Clinical improvement (CI)	At least one of the following for at least 8 weeks, in the absence of progressive disease, or complete or partial remission: • ≥ 2 g/dL increase in hemoglobin or achievement of transfusion independence (only applies to patients with baseline hemoglobin ≤ 10 g/dL) (3) • ≥ 50% reduction in palpable splenomegaly (if spleen ≥ 10 cm at baseline) OR spleen no longer palpable (if 5 - 10 cm at baseline) (4) • ≥ 100% increase in platelet count AND platelet count ≥ 50 x10^9/L (only applies to patients with baseline platelet count < 50 x10^9/L) • ≥ 100% increase in neutrophil count AND neutrophil count ≥ 0.5 x10^9/L (only applies to patients with baseline neutrophil count < 1.0 x10^9/L)
Progressive disease (PD)	At least one of the following: (5) • Progressive splenomegaly: palpable splenomegaly > 5 cm below left costal margin if no prior palpable splenomegaly, OR ≥ 100% increase in palpable splenomegaly if baseline 5 - 10 cm, OR ≥ 50% increase if baseline splenomegaly > 10 cm • Leukemic transformation confirmed by bone marrow blast count ≥ 20% • ≥ 20% increase in peripheral blood blast percentage lasting for ≥ 8 weeks
Stable disease	None of the above
Relapse	Patient previously meeting criteria CI, PR or CR no longer meets criteria for CI

Notes

(1) Because peripheral blood film analysis is subjective, CR does not require absence of morphologic abnormalities of red cells, platelets, and neutrophils

(2) In patients with CR and a pre-existing cytogenetic abnormality, complete cytogenetic response is defined as failure to detect the abnormality in at least 20 metaphases. Partial cytogenetic response is defined as ≥ 50% reduction in abnormal metaphases. Major molecular response is defined as absence of a previously-positive specific disease-associated mutation in peripheral blood.

(3) Transfusion-dependence is defined as a transfusion of at least 2 units of red blood cells in the previous month for a hemoglobin < 8.5 g/dL not due to clinically overt bleeding. During therapy within clinical trials, transfusions for a hemoglobin ≥ 8.5 g/dL is therefore discouraged unless clinically indicated.

(4) In splenectomized patients, palpable hepatomegaly is substituted, with the same measurement criteria.

(5) Worsening cytopenias were not included as a criterion for progressive disease because of the difficulty differentiating between disease-associated cytopenias and drug-induced myelosuppression. However, ≥ 2 g/dL decrease in hemoglobin, ≥ 100% increase in transfusion requirement, or new development of transfusion dependence, each lasting for > 3 months after discontinuation of protocol therapy, can be considered disease progression.

Polycythemia Vera(60)

	Criteria
Complete remission	
A	**Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND**
B	**Durable* peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count ≤400 × 10^9/L, WBC count <10 × 10^9/L, AND**
C	**Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND**
D	**Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of >grade 1 reticulin fibrosis**
Partial remission	
A	**Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND**

	Criteria
B	**Durable[*] peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count ≤400 × 10^9/L, WBC count <10 × 10^9/L, AND**
C	**Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND**
D	**Without bone marrow histological remission defined as persistence of trilinear hyperplasia.**
No response	**Any response that does not satisfy partial remission**
Progressive disease	**Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia[‡]**

Molecular response is not required for assignment as complete response or partial response. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a preexisting abnormality. Partial response applies only to patients with at least 20% mutant allele burden at baseline. Partial response is defined as ≥ 50% decrease in allele burden.
WBC, white blood cell.
[*]Lasting at least 12 wk.
[†]Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.[10]
[‡]For the diagnosis of post-PV myelofibrosis, see the IWG-MRT criteria[12]; for the diagnosis of myelodysplastic syndrome and acute leukemia, see WHO criteria.

CMML(61)

Complete response (presence of all of the following improvements)*
Bone marrow: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis)¶
Peripheral blood[Δ]
WBC ≤10 x 10^9 cells/L
Hgb ≥11 g/dL
Platelets ≥100 x 10^9/L; ≤450 x 10^9/L
Neutrophils ≥1.0 x 10^9/L

Blasts 0%
Neutrophil precursors reduced to ≤2%
Monocytes ≤1 x 10^9/L
Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Provisional category of CR with resolution of symptoms:$^{\Delta}$ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*
Complete cytogenetic remission
Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic syndrome, myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH$^{\Diamond}$
Partial remission
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity *except* in cases of MDS/MPN with ≤5% bone marrow blasts at baseline
Marrow response
Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above
Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, *or* reduction in grading of reticulin fibrosis from baseline on at least two bone marrow evaluations spaced at least two months apart
Clinical benefit
Requires one of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥8 weeks) to be considered a clinical benefit
Erythroid response

Hgb increase by ≥2.0 g/dL
TI for ≥8 weeks for patients requiring at least four packed red blood cell transfusions in the previous eight weeks
Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation§
Platelet response
Transfusion independence when previously requiring platelet transfusions of at least a rate of four platelet transfusions in the previous eight weeks
Pretreatment ≤20 x 10^9/L: Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100%
Pretreatment >20 x 10^9/L but ≤100 x 10^9/L: Absolute increase of ≥30 x 10^9/L§
Neutrophil response
Pretreatment ≤0.5 x 10^9/L at least 100% increase and an absolute increase ≥0.5 x 10^9/L
Pretreatment >0.5 x 10^9/L and ≤1.0 x 10^9/L at least 50% increase and an absolute increase ≥0.5 x 10^9/L§
Spleen response
Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
Symptom response
Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit¥

CMML: chronic myelomonocytic leukemia; CR: complete response; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; WBC: white blood cell; Hgb: hemoglobin; FISH: fluorescence in situ hybridization; TI: transfusion independence; MPN-SAF TSS: Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; MDS IWG: Myelodysplastic Syndrome International Working Group.
* Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.
¶ If there is no significant fibrosis present on the initial bone marrow biopsy, a second

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biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.
Δ Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.
◊ Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.
§ Resolution of abnormal peripheral blood counts must persist for at least two separate analyses over at least eight weeks. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150 to 450 x 10^9/L) and resolution of leukocytosis to WBC ≤10 x 10^9 cells/L but ≥1.5 x 10^9/L. Hgb should be maintained >11 g/dL and platelets ≥100 x 10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤2 to 3%) and/or 1 x 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.
¥ MPN-SAF TSS validation among patients with MDS/MPN is currently under way (RA Mesa, personal communication, 2014).