2546.00: Donor Statin Treatment for Prevention of Severe Acute GVHD after Nonmyeloablative Hematopoietic Cell Transplantation

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Donor Statin Treatment for Prevention of Severe Acute GVHD after Nonmyeloablative Hematopoietic Cell Transplantation

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ABBREVIATIONS

AABB	American Association of Blood Banks
ABW	actual body weight
AE	adverse event
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ALT	alanine amino transferase
AST	aspartate amino transferase
β-HCG	beta human chorion gonadotropin
BMT	bone marrow transplantation
BSA	body surface area
BU	busulfan
CAT	computed axial tomography
CCO	Clinical Coordinator Office
CI	confidence interval
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete remission
CSP	cyclosporine
Css	concentration at steady state
CTCAE	common toxicity criteria for adverse events
CTN	Clinical Trials Network
CXR	chest x-ray
CY	cyclophosphamide
DFS	disease-free survival
DLCO	Diffusion capacity of lung—carbon monoxide
DSMB	data and safety monitoring board
DSMP	data and safety monitoring plan
ECOG	Eastern Cooperative Oncology Group
EKG	electrocardiogram
EMG	electromyogram
FACT	Foundation for the Accreditation of Cellular Therapy
FEF	forced expiratory flow
FEV1	forced expiratory volume in 1 second
FHCRC	Fred Hutchinson Cancer Research Center
FLU	fludarabine
FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
HCT	hematopoietic cell transplantation
HIV	Human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio

HRPP	human research protection plan
HTLV	human T cell lymphotropic virus
IBW	ideal body weight
IRB	institutional review board
IRO	Institutional Review Office
IST	immunosuppressive treatment
MDS	myelodysplastic syndrome
MESNA	sodium-2-mercapto ethane sulfonate
MMF	mycophenolate mofetil
MTX	methotrexate
MUGA	Multiple gated acquisition
NIH	National Institutes of Health
NCI	National Cancer Institute
NRM	non-relapse mortality
OS	overall survival
OWL	optical web library
PBSC	peripheral blood stem cell
PCR	polymerase chain reaction
PFT	pulmonary function tests
PI	principal investigator
RV	residual volume
SAE	serious adverse event
SCCA	Seattle Cancer Care Alliance
TAC	Tacrolimus
TBI	total body irradiation
UPN	unique patient number
URD	unrelated donor
UW	University of Washington

INTRODUCTION

This **document** is a clinical research protocol that will be conducted in compliance with Federal regulations and all applicable Institutional Review Board (IRB) requirements. This protocol builds on seminal observations from 2 previous studies.

In two retrospective analyses of outcomes among 1206 recipients of HLA-matched HCT [1,2], we found:

- Statin use by HLA-identical sibling donors was associated with profound protection against severe acute GVHD. GVHD-protection was not offset by increased relapse rates.
- Recipient statin use beyond day 100 after transplant was associated with a reduced risk of chronic GVHD at the expense of an increased risk of relapse.
- GVHD-protective effects were restricted to patients given CSP-based postgrafting immunosuppression and not observed among those given TAC.
- GVHD-protective effects were most pronounced in the gastrointestinal tract.

Based on the favorable outcomes associated with donor statin use in the retrospective analyses, the present study seeks to confirm these finding prospectively. Specifically, we propose to treat HLA-identical related donors with atorvastatin for 2 weeks prior to collection of PBSC aimed at reducing the risk of severe acute GVHD in recipients after nonmyeloablative HCT.

BACKGROUND

2.1 Immunomodulatory effects of statins.

In recent years, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or "statins", have been shown to alter immune function in ways that may contribute to their anti-atherosclerotic effects. Statins also appear to reduce immune responses to autoantigens and alloantigens [3-6]. The best characterized activity of statins involves inhibition of mevalonate and cholesterol biosynthesis, which is mediated by binding to HMG-CoA reductase. Blocking mevalonate production, however, also inhibits the synthesis of intermediates required for isoprenylation of GTP-binding cell signaling proteins such as Ras, Rac and Rho, thereby disrupting intracellular signaling pathways [6-9]. Immune functions shown to be promoted by statins are Th2-polarization[1] and expansion of regulatory T cells (Treg) [10]. At the same time statins inhibit lymphocyte trafficking to sites of inflammation [11-13], antigen-presenting cell (APC) function [14,15], and the development of Th_{17} cells [16]. While statin-mediated changes in immune function have been studied extensively, the potential immunosuppressive synergism between statins and calcineurin inhibitors has not been examined.

2.2 Statins for GVHD-prevention: Preclinical and clinical studies

Zeiser et al. observed a significantly reduced mortality related to acute GVHD when either donor or recipient mice were given atorvastatin for 10 days before major histocompatibility complex (MHC)-mismatched allogeneic HCT [3]. This study also showed that statin-mediated protection against GVHD was due to parallel effects on T cells and APC, and that therapy did not simply

suppress T cell responses in general, as the ability of the transplanted T cells to kill tumor cells (GVT effect) was preserved.

In a recent retrospective analysis of 67 patients who received HLA-matched or mismatched related or unrelated allografts for treatment of hematologic malignancies, Hamadani et al. found a trend towards a decreased risk of grade 2-4 acute GVHD (10% versus 40%; p=0.08) among the 10 recipients who were under treatment with a statin at the time of HCT, compared to those who were not [17]. In this analysis, however, the authors did not account for donor statin exposure, and definitive conclusions were limited by small sample size and heterogeneity of the patient population.

Most pertinent to the design of the present study was the observation that **donor statin use was associated with protection against severe acute GVHD after HCT from HLA-identical related donors** [1]. In retrospective analysis (n=567), we found that compared to allografts where neither the donor nor recipient used a statin at the time of transplant (n=464), statin use by the donor and not the recipient (n=75) was associated with a profoundly decreased risk of grade 3-4 acute GVHD (multivariate hazard ratio [HR], 0.28; 95% confidence interval [CI], 0.1-0.9; p=0.03) (**Table 1**). Statin use by both donor and recipient (n=12) was suggestively associated with a decreased risk of grade 3-4 acute GVHD (HR, 0.00; 95% CI, undefined; p=0.06), while statin use by the recipient and not the donor (n=16) did not confer protection against acute GVHD. Donor statin-treatment was associated with significant protection against acute GVHD in the gastrointestinal tract (p=0.02) but not in the skin. Surprisingly, statin-associated GVHD-protection was restricted to recipients with CSP-based postgrafting immunosuppression (n=417; 74%; HR, 0.0; 95% CI, undefined; p<0.0001) and was not observed among those given TAC (significance of effect modification: CSP vs. TAC, p=0.009). The unexpected effect association between statins and CSP raises the question whether the two

Table 1: Multivariate analyses for association of recipient and donor statin use with various outcomes.*

	All patients (n=567)						Patients with CSP-based GVHD-prophylaxis (n=417)					
	(R+/D-, n=16)		(R-/D+, n=75)		(R+/D+, n=12)		(R+/D-, n=13)		(R-/D+, n=54)		(R+/D+, n=10)	
Endpoint	**HR* (95% CI)**	**p***	**HR (95% CI)**	**p**	**HR* (95% CI)**	**p***	**HR* (95% CI)**	**p***	**HR* (95% CI)**	**p***	**HR* (95% CI)**	**p***
Grade 2-4 GVHD	1.01 (0.5-2.0)	0.98	0.89 (0.6-1.2)	0.47	**0.33 (0.1-1.0)**	**0.06**	1.10 (0.5-2.3)	0.79	0.79 (0.5-1.2)	0.23	**0.22 (0.1-0.9)**	**0.03**
Grade 3-4 GVHD	1.78 (0.6-5.0)	0.28	**0.28 (0.1-0.9)**	**0.03**	**0.00 (undef.)**	**0.06**	1.76 (0.6-5.0)	0.29	**0.00 (undef)**	**<0.0001**	**0.00 (undef.)**	**0.06**
Chronic GVHD	0.93 (0.5-1.8)	0.83	0.82 (0.6-1.2)	0.26	0.58 (0.3-1.3)	0.19	0.79 (0.4-1.6)	0.53	0.94 (0.6-1.4)	0.76	0.59 (0.2-1.5)	0.25
Relapse/ disease prog.	0.97 (0.4-2.7)	0.96	0.63 (0.4-1.1)	0.11	0.74 (0.2-3.0)	0.67	1.27 (0.4-3.6)	0.66	0.72 (0.4-1.3)	0.30	1.04 (0.3-4.3)	0.95
NRM	0.45 (0.2-1.2)	0.12	0.72 (0.4-1.2)	0.17	0.66 (0.2-2.0)	0.49	0.36 (0.1-1.1)	0.08	0.67 (0.4-1.2)	0.15	0.86 (0.3-2.7)	0.80
Overall mortality	0.58 (0.3-1.2)	0.16	0.73 (0.5-1.1)	0.10	0.77 (0.3-1.9)	0.56	0.53 (0.2-1.2)	0.14	0.75 (0.5-1.1)	0.18	1.00 (0.4-2.5)	0.99

Outcomes are shown for all patients (n=567; left table) and for patients with CSP-based GVHD-prophylaxis (n=417; right table). Outcome estimates are in comparison to controls where both donor *and* recipient did *not* receive statin treatment at the time of HCT (n=464 for "all patients" and n=340 for patients with CSP-based GVHD-prophylaxis). *Adjusted for: Sex-mismatch, conditioning intensity, donor age >50 years, patient age >50 years, and disease risk. Abbreviations pertaining to statin treatment at the time of transplant: R-/D-: neither recipient nor donor; R+/D-, recipient only; R-/D+, donor only; R+/D+, both recipient and donor.

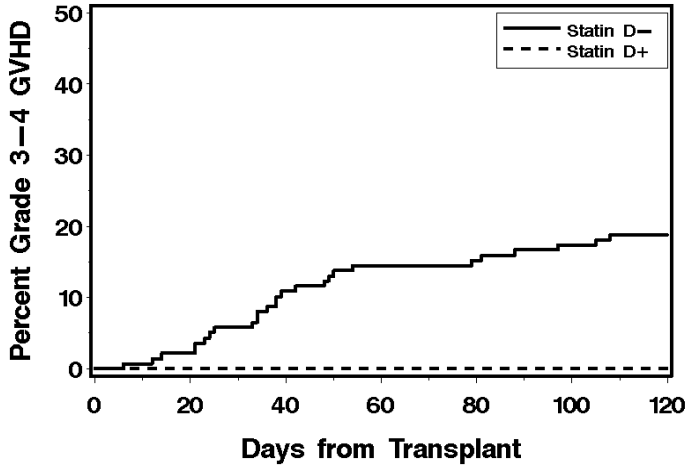
drugs share a cellular target that accounts for the observed immunosuppressive synergism.

GVHD-protection associated with donor statin use was not offset by increased rates of recurrent malignancy. An increased risk of recurrent malignancy and a reduced risk of chronic GVHD were only observed among recipients of HLA-matched related and unrelated grafts (n=1206)

who were given statins beyond day 100 after transplant [2]. Overall, these results suggest that donor statin treatment (without recipient statin treatment) may be a promising strategy for preventing severe acute GVHD without compromising immunologic control of the underlying malignancy.

The retrospective analysis also showed that favorable outcomes associated with donor statin use were not confined to a specific type of conditioning intensity but seen after both nonmyeloablative and myeloablative HCT. **Figure 1** shows the cumulative incidence of grade 3-4 acute GVHD among recipients of nonmyeloablative HCT from HLA-matched donors who has CSP-based immunosuppression according to donor statin use. This subgroup analysis shows that donor statin treatment has promise to substantially reduce the risk of severe acute GVHD and thereby NRM without compromising control of the underlying malignancy.

Figure 1: ***Cumulative incidence of grade 3-4 acute GVHD after nonmyeloablative hematopoietic cell transplantation at the Fred Hutchinson Cancer Research Center (2001-2007) according to donor statin use.*** *The analysis was restricted to patients who had CSP-based immunosuppression after transplant (n=162).*



2.3 Rationale for the Current Study

Based on the favorable outcomes associated with donor statin use in the retrospective analyses, the present study seeks to confirm these finding prospectively. Specifically, we propose to treat HLA-identical related donors with atorvastatin during 2 weeks prior to collection of peripheral blood stem cells (PBSC) aimed at reducing the risk of severe acute GVHD in recipients. Since the statin-mediated GVHD-protective effect was only seen among patients who had CSP-based immunosuppression and not among those given TAC, recipients enrolled in the present study will receive an immunosuppressive regimen that includes CSP. The study may be offered either as an independent protocol that includes donor statin-treatment and the nonmyeloablative preparative regimen (low-dose TBI and fludarabine) or in conjunction with a designated separate transplant investigational protocol that uses a nonmyeloablative preparative regimen, provided the respective transplant protocol does not use acute GVHD as the primary endpoint.

STUDY OBJECTIVES

3.1 Primary Objective

To assess whether 2 weeks of donor statin treatment reduces the risk of severe acute GVHD.

3.2 Secondary Objective

To assess whether 2 weeks of statin treatment of normal PBSC donors is feasible, tolerable and safe.

STUDY DESIGN

4.1 Description of Study

This is a multi-center, single-arm, phase II study, with plans to enroll a maximum of 100 patients. This study may be an adjunct to a nonmyeloablative protocol or treatment plan, or may be a primary treatment protocol. For Outside Centers, it will be used as an adjunct only.

4.2 Endpoints

Primary Endpoint

The primary endpoint is grade 3-4 acute GVHD

Secondary Endpoints

Secondary endpoints include the following

- Grades II-IV acute GVHD
- Proportion of patients requiring secondary systemic immunosuppressive therapy
- Chronic extensive GVHD
- Recurrent or progressive malignancy
- Non-relapse mortality at 1 year
- Overall survival
- Proportion of donors who have to discontinue atorvastatin because of toxicity

PATIENT SELECTION

5.1 Inclusion Criteria (If Protocol 2546 serves as an adjunct protocol, the patient only needs to meet inclusion criteria 1 through 5A.)

1) Availability of HLA-identical sibling donor
2) Transplantation with PBSC
3) CSP-based postgrafting immunosuppression

4) Willingness to give informed consent
5) **A.** Patient is enrolled on an investigational nonmyeloablative HCT protocol or a nonmyeloablative treatment plan with postgrafting CSP that does not use acute GVHD as its primary endpoint (protocol 2546 serves as adjunct protocol).

   or

   B. Patient is **not** enrolled on an investigational nonmyeloablative HCT protocol, in which case protocol 2546 serves as an independent primary treatment protocol and the patient must meet the following inclusion and exclusion criteria:

   a. Patients must have a hematologic malignancy treatable by nonmyeloablative HCT. The following diseases will be permitted although other diagnoses can be considered if approved by PCC and the principal investigator:
      - Aggressive non-Hodgkin lymphomas (NHL) and other histologies such as diffuse large B-cell NHL – not eligible for autologous HCT, not eligible for high-dose allogeneic HCT, or after failed autologous HCT.
      - Mantle-cell NHL - may be treated in first CR. (Diagnostic LP required pre-transplant)
      - Low grade NHL – with <6 month duration of CR between courses of conventional therapy
      - CLL – must have either:
        i. failed to meet NCI Working Group criteria for complete or partial response after therapy with a regimen containing FLU (or another nucleoside analog) or experience disease relapse within 12 months after completing therapy with a regimen containing FLU (or another nucleoside analog);
        ii. failed FLU-CY-Rituximab (FCR) combination chemotherapy at any time point; or
        iii. have “17p deletion” cytogenetic abnormality. Patients should have received induction chemotherapy but could be transplanted in 1st CR;
        iv. Patients with a diagnosis of CLL (or small lymphocytic lymphoma) that progresses to prolymphocytic leukemia (PLL); or
        v. patients with T-cell CLL or PLL.
      - Hodgkin lymphoma – must have received and failed frontline therapy.
      - Multiple myeloma – must have received prior chemotherapy. Consolidation of chemotherapy by autografting prior to nonmyeloablative HCT is permitted.
      - Acute myeloid leukemia (AML) – must have < 5% marrow blasts at the time of transplant.
      - Acute lymphocytic leukemia (ALL) – must have <5% marrow blasts at the time of transplant.
      - Chronic myeloid leukemia (CML) – Patients will be accepted if they have shown intolerance to tyrosine kinase inhibitors or are beyond CP1 and if they have received previous myelosuppressive chemotherapy or HCT, and have <5% marrow blasts at time of transplant.
      - Myelodysplasia (MDS)/ myeloproliferative syndrome (MPS) – Patients must have <5% marrow blasts at time of transplant.
      - Waldenstrom’s macroglobulinemia **–** must have failed 2 courses of therapy.

b. Patients <12 years of age must be approved by the principal investigator and by a relevant patient review committee, such as the FHCRC Patient Care Conference (PCC).
c. Patients must have either relapsed after previous high-dose chemotherapy and autologous or allogeneic HCT, or else be ineligible for such an approach due to age, failure to mobilize sufficient hematopoietic stem cells, medical comorbidities, or patient refusal (see *d.* below).
d. Patients who refuse to be treated on a conventional autologous or allogeneic HCT protocol.

5.2 Exclusion Criteria (If Protocol 2546 serves as an adjunct protocol, the patient only needs to meet exclusion criteria 1 through 3.)

1) Myeloablative preparative regimen.
2) Participation in an investigational study that has acute GVHD as the primary endpoint.
3) The allogeneic PBSC donor has a contraindication to statin treatment.
4) Patients eligible for and willing to receive potentially curative high-dose chemotherapy and autologous HCT.
5) Patients with the following levels of organ dysfunction are ineligible:
   i. Cardiac: Cardiac ejection fraction <30% on MUGA scan or cardiac echo or active symptomatic coronary artery disease. Patients with cardiac disease should be evaluated with appropriate cardiac studies and/or cardiology consultation as clinically indicated.
   ii. Pulmonary: $DLCO_{corrected}$ <40% of predicted, TLC < 30% of predicted, FEV_1 <30% of predicted, or receiving continuous supplementary oxygen.
   iii. Hepatic: Patients with clinical or laboratory evidence of liver disease should be evaluated in conjunction with the GI consult service for the cause of the liver disease, its clinical severity, and the degree of portal hypertension. Patients will be excluded if they are found to have fulminant liver failure, cirrhosis of the liver with evidence of portal hypertension, bridging fibrosis, alcoholic hepatitis, esophageal varices, a history of bleeding esophageal varices, hepatic encephalopathy, refractory ascites related to portal hypertension, bacterial or fungal liver abscess, chronic viral hepatitis with total serum bilirubin >3mg/dl, or actively symptomatic biliary disease.
   iv. Renal: Patients with renal failure are eligible. However, patients with pre-existing renal insufficiency will likely have further compromise in renal function and may require dialysis.
6) Patients who are seropositive for human immunodeficiency virus (HIV).
7) Women who are pregnant or breast-feeding.
8) Fertile men or women unwilling to use contraception during HCT and for 12 months afterward.
9) Patients with active non-hematological malignancies (except non-melanoma skin cancers) or those with non-hematological malignancies (except non-melanoma skin cancers) who have been rendered with no evidence of disease, but have a greater than 20% chance of having disease recurrence within 5 years. This exclusion does not apply to patients with non-hematologic malignancies that do not require therapy.
10) Karnofsky score <60 for adult patients.
11) Lansky-Play Performance Score <50 for pediatric patients.
12) Patients with fungal pneumonia with radiological progression after receipt of amphotericin formulation or mold-active azoles for greater than 1 month.

DONOR SELECTION

6.1 Inclusions

1) Age ≥ 18 years
2) HLA genotypically identical sibling
3) Willingness to give informed consent

6.2 Exclusions

1) Age < 18 years
2) History of liver disease. A donor with a history of liver disease would be eligible if the serum ALT or AST are <2 times ULN.
3) History of myopathy
4) Hypersensitivity to atorvastatin
5) Pregnancy
6) Nursing mother
7) Current serious systemic illness
8) Concurrent treatment with strong inhibitors of hepatic CYP 3A4 (i.e. clarithromycin, erythromycin, protease inhibitors, azole antifungals)
9) Failure to meet local criteria for stem cell donation
10) Total creatinine kinase > 2 times the ULN

INFORMED CONSENT OF SUBJECT AND DONOR

Patients will be referred to the SCCA or appropriate outside center institution for consideration of a growth factor-mobilized blood cell transplant. Both patient and the related donor will be completely evaluated. The protocol will be discussed thoroughly with patient, donor and family, and all known risks to patient and donor will be described. The procedure and alternative forms of therapy will be presented as objectively as possible and the risks and hazards of the procedure explained to the patient and donor or, in the case of minors, to responsible family members. Consent will be obtained using forms approved by the local IRB. A summary of the conference will be dictated for the medical record detailing what was covered.

PATIENT AND DONOR REGISTRATION

Eligible FHCRC donor/recipient pairs will be identified by the Clinical Coordinators Office (CCO) (Intake Office) and assigned UPNs (Unique Patient Numbers). The Data Management Office will register donors and recipients on to the protocol through the Data Management Office. For patients enrolled at external sites, they will be registered to this study by FHCRC study staff.

PLAN OF TREATMENT

9.1 Donor Treatment with Atorvastatin

- Eligible donors will be given **atorvastatin** (generic drug preferred, if available; otherwise Lipitor™) **40 mg/day orally starting on day -14**. The last dose of atorvastatin will be

administered in the morning of the last day of stem cell collection (total of 15 doses).

- The following guidelines are to be followed if the day of transplant must be re-scheduled while the donor has already started atorvastatin treatment:
    - Transplant moved up: If the transplant date needs to be moved up by ≤ 3 days, a shortened atorvastatin treatment course is permissible provided at least 12 days of treatments (40 mg/day) can be given to the donor. If the transplant needs to be moved up for > 3 days, atorvastatin treatment of the donor will be discontinued and patients will not be followed with respect to the primary endpoint of this study.
    - Transplant delayed: If the transplant date needs to be delayed, an extended atorvastatin treatment course is permissible provided the new transplant date is already agreed upon and lies within 14 days from the date the decision to re-schedule was made. If the re-scheduled transplant date lies beyond 14 days from the date the decision to re-schedule is made, the donor will discontinue atorvastatin treatment and resume statin treatment on day -14 before the new transplant date.

9.2 Recipient Treatment (References below to standard practice refer to standard practice at site where HCT is being performed.)

- If the patient is enrolled on an investigational nonmyeloablative HCT protocol or a treatment plan that uses a nonmyeloablative preparative regimen with postgrafting CSP that does not use acute GVHD as its primary endpoint, the preparative regimen and immunosuppression after transplant will be according to respective protocol or treatment plan (protocol 2546 serves as adjunct protocol).

- **If the patient is not enrolled on an investigational nonmyeloablative HCT protocol or a treatment plan that uses a nonmyeloablative preparative regimen, protocol 2546 serves as an independent primary treatment protocol. The preparative regimen and immunosuppression after transplant will be as follows, see figure 2:**

Treatment may be initiated in the outpatient department, and patients will be admitted to the hospital if medically necessary to address transplant-related complications or other medical issues.

TBI Criteria for 2546 as a Primary Protocol:

***Criteria for 3 Gy TBI (only for patients in Regimen A, Flu/TBI):**
Patients need to fulfill one or more of the following criteria for 3 Gy TBI:
a) Patients with MDS, MPD, CML, or other hematologic malignancies not previously treated with myelosuppressive chemotherapy.
b) Patients who had a previous allogeneic transplant.
c) Patients who had a prior syngeneic transplant without subsequent myelosuppressive chemotherapy.
d) Patients who have not had myelosuppressive chemotherapy within 3-6 months of HCT may be at higher risk of rejection depending on treatment history and underlying diagnosis. Confirm TBI dose (2 vs 3 Gy) with PI.

TBI Criteria for 2546 as an adjunct Protocol:

***Criteria for 4 Gy TBI:**
Patients on Protocol 2546 as an adjunct protocol, TBI doses can exceed > 3 Gy when the protocol serves as adjunct to a reduced intensity treatment plan that includes 4 Gy TBI.

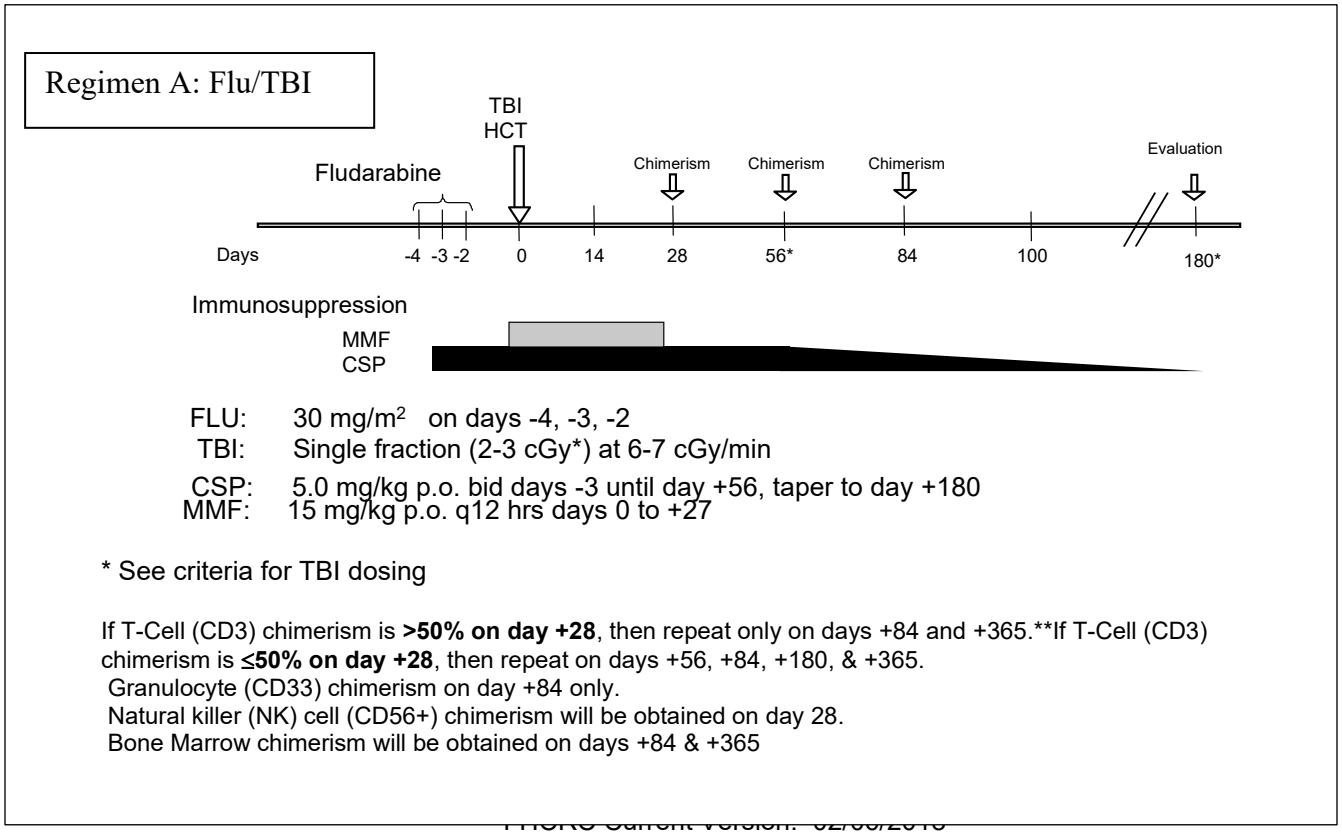
A. For 2546 as a Primary Protocol: Preparative Regimen and Postgrafting Immunosuppression

a) Fludarabine 30 mg/m^2/day IV on days -4, -3, and -2 (except for patients who had prior autologous HCT or equivalent high-dose therapy without HCT) within 6 months.
b) Total body irradiation, 2-3 Gy* (6-7 cGy/min; linear accelerator), on day 0
c) Infusion of hematopoietic allograft on day 0
d) Post-grafting immunosuppression:
   i. CSP, 5 mg/kg PO q12 hrs from day -3 to day +56, then tapered to day +180

      Age ≤ 6 years: 2 mg/kg IV every 8 hours
      Age > 6 years: 2 mg/kg IV every 12 hours

   ii. MMF, 15mg/kg PO/IV q12 hrs from day 0 to day +27

Figure 2. Diagram of Treatment Plan



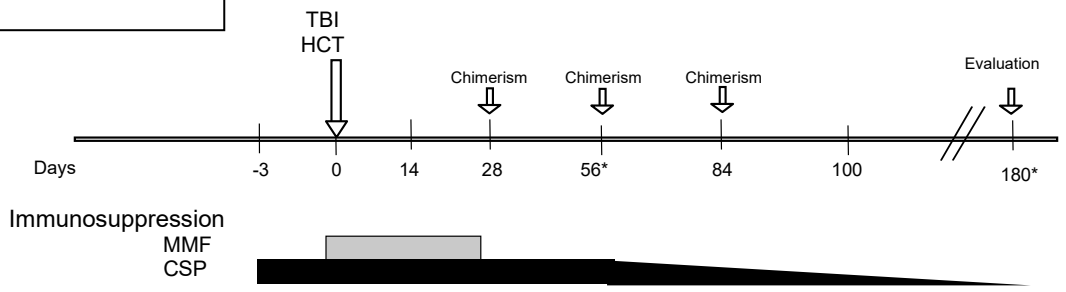
FLU: 30 mg/m^2 on days -4, -3, -2
TBI: Single fraction (2-3 cGy*) at 6-7 cGy/min
CSP: 5.0 mg/kg p.o. bid days -3 until day +56, taper to day +180
MMF: 15 mg/kg p.o. q12 hrs days 0 to +27

* See criteria for TBI dosing

If T-Cell (CD3) chimerism is **>50% on day +28**, then repeat only on days +84 and +365.**If T-Cell (CD3) chimerism is ≤**50% on day +28**, then repeat on days +56, +84, +180, & +365.
Granulocyte (CD33) chimerism on day +84 only.
Natural killer (NK) cell (CD56+) chimerism will be obtained on day 28.
Bone Marrow chimerism will be obtained on days +84 & +365

(See Patient Post-Transplant Evaluation for more instructions and exceptions).
Treatment starts on Day -4

Regimen B: TBI Alone



TBI: Single fraction (2 cGy) at 6-7 cGy/min
CSP: 5.0 mg/kg p.o. bid days -3 until day +56, taper to day +180
MMF: 15 mg/kg p.o. q12 hrs days 0 to +27

If T-Cell (CD3) chimerism is **>50% on day +28**, then repeat only on days +84 and +365.*If T-Cell (CD3) chimerism is **≤50% on day +28**, then repeat on days +56, +84, +180, & +365.
Granulocyte (CD33) chimerism on day +84 only.
Natural killer (NK) cell (CD56+) chimerism will be obtained on day 28.
Bone Marrow chimerism will be obtained on days +84 & +365
(See Patient Post-Transplant Evaluation for more instructions and exceptions).
Treatment starts on Day -3

B. Peripheral Blood Stem Cell Infusion

G-CSF-mobilized PBSC from an HLA-identical related donor will be the source of hematopoietic stem cells. Two 12-liter leukaphereses on consecutive days, day -1 and day 0, will be obtained, and cells will be infused together on day 0 after TBI. Refer to institutional practice guidelines for methods of infusion. If the $CD34^+$ cell dose is <5.0 x 10^6/kg recipient weight after the second collection, a third day collection should be added, with an extra dose of G-CSF given to the donor before the final collection.

C. Adjustment of Post-grafting Immunosuppression

Immunosuppression after transplant will be with MMF and CSP, as described above. CSP and MMF doses should be based on adjusted body weight. If actual weight is less than ideal weight, then actual body weight will be used. MMF will be initiated on day 0, with the first dose given 4–6 hours after allograft infusion is complete. In the absence of GVHD, CSP and MMF will be tapered and/or discontinued as described above. In the presence of GVHD, standard institutional recommendations for acute GVHD therapy should be followed. In the event of progression or recurrence of malignancy, and in the absence of GVHD, CSP and MMF may be tapered more rapidly to stimulate a graft-vs.-malignancy effect, at the discretion of the attending physician. Investigational medications aimed at treating relapse or GVHD after transplant are permissible.

- ***Guidelines for CSP Administration and Monitoring***

If there is nausea and vomiting at anytime during CSP treatment, consideration should be given to administering CSP intravenously at the appropriate dose that was used to

obtain a therapeutic level. For pediatric patients, it is recommended that CSP dosing be initiated using the IV formulation and then converted to PO when tolerated. The appropriate dose conversion from PO to IV and IV to PO should be discussed with the transplant pharmacist. Blood pressure, renal function and electrolytes (including magnesium) should be followed at least 3 times per week during the first month, twice weekly until day +100, then once per week until CSP is stopped.

CSP Dose Adjustments: Initial high Cyclosporine (CSP) doses are required based on the preclinical nonmyeloablative canine studies, which used an equivalent dose to establish an allograft. After day +28, CSP levels typical for unrelated HCT will be targeted. Dose reduction should only be made if CSP toxicity is present, and/or levels exceed values provided in Table 2. There are two methods for calculating CSP levels. Table 2 provides desired levels for specific methods. To avoid inadequate immune suppression, dose reductions should be conservative. Therapeutic levels of CSP should be maintained.

Table 2: CSP Dose Adjustment

	CSP Level to Target Using LC-MS/MS Method	**CSP Level to Target Using Immunoassay Method**
Day "0" – Day +28 Whole blood "trough" (11-12 hrs from prior dose)	400 ng/ml	500 ng/ml (upper end therapeutic range for this method)
After Day +28	120 - 360 ng/ml	150 - 450 ng/ml
Levels >480 ng/ml by LC-MS/MS Method • **with or without CSP toxicity** • **decrease GFR ≥50%** • **increase creatinine 2x baseline due to CSP**	25% dose reduction	N/A
Levels >600 ng/ml by Immunoassay Method • **with or without CSP toxicity** • **Decrease GFR ≥50%** • **increase creatinine 2x baseline due to CSP**	N/A	25% dose reduction
Patients on Hemodialysis	320 ng/ml	400 ng/ml

- ***Guidelines for MMF Administration and Monitoring***

If there is nausea or vomiting at any time preventing the oral administration of MMF, the drug should be administered intravenously. It will be left to the discretion of the pediatric

attending whether to initiate MMF dosing IV or PO. The PO to IV or IV to PO dose conversion should be discussed with the transplant pharmacist. If clinical judgment suggests observed toxicities are related to MMF, the dose may be adjusted. The adjustment or discontinuation of MMF at any point should be discussed with the PI and documented in the permanent medical record and all Case Report Forms (CRF).

D. Collection of Donor PBSC

- **G-CSF Administration to Donors:**

G-CSF will be administered by subcutaneous daily injections from day -4 to day 0 at a dose of 16 µg/kg/day for 5 consecutive days. The schedule of G-CSF administration and PBSC collections should be confirmed with the personnel in the apheresis room. Day 0 should be scheduled on a Tuesday-Thursday, if possible (FHCRC patients only).

- **PBSC Collection:**

Donors will preferably undergo vein-to-vein collections, or may receive an appropriate catheter inserted on or before the day of apheresis. PBSCs will be collected on the afternoon of day -1 and stored in the refrigerator at 4ºC overnight. A second collection will be performed the following afternoon and both collections will be infused on day 0. If $<5x10^6$ $CD34^+$ cells/kg recipient weight are collected, an additional (third) day of collection should be performed. If PBSC cannot be collected by a vein-to-vein technique, a percutaneous Mahurkar catheter will be inserted. General procedures will include the use of a standard apheresis machine (COBE Spectra, Lakewood Colo.), and processing up to 16 liters of whole blood during the collection.

Table 3: Treatment Schema for HLA-Identical Related Donors

Days	-4	-3	-2	-1	0
G-CSF 16 µg/kg/SQ	X	X	X	X	X
G-PBMC collection				X	X

Immunophenotyping of the G-PBMC product will be performed by the cryobiology laboratory and will include T-cells and their subsets, monocytes, and NK cells.

E. ABO-Incompatibility

All patients with ABO incompatibility should be evaluated and treated according to institutional standard practice.

F. Post-transplant Growth Factors

In general, patients should not receive post-transplant growth factors during the first 3 weeks after transplant. Growth factors should not be given unless neutropenia (ANC <500/μL) persists past day +21 after transplant.

G. Infection Prophylaxis

Patients will receive monitoring for and prophylaxis against viral, bacterial, and fungal infections per institutional standard practice.

H. Evaluation of Chimerism

Definitions: For the purposes of this protocol, the following definitions will apply: For the purposes of this protocol, *mixed chimerism* will be defined as the detection of donor T cells (CD3+) and granulocytes (CD 33+), as a proportion of the total T cell and granulocyte population, respectively, of greater than 5% and less than 95% in the peripheral blood. *Full donor chimerism* is defined as > 95% donor CD3+ T cells. Mixed or full donor chimerism will be evidence of *donor engraftment. Increasing donor chimerism* is defined as an absolute increase of 20% of CD3+ T cells over the previous chimerism evaluation. *Decreasing donor chimerism* is defined as an absolute decrease of 20% of CD3+ T cell chimerism over the previous month. Low donor chimerism is defined as < 40% CD3+ T cells after HCT. Low donor chimerism should always be confirmed with repeat peripheral blood T cell and granulocyte chimerism analysis. A DNA-based assay that compares the profile of amplified fragment length polymorphisms (ampFLP) (or FISH studies or VNTR) of the patient and donor will be used to quantitate chimerism of sorted peripheral blood T-cells (CD3+) and granulocytes (CD 33+). The same assay should be used in a given patient for repeated studies of chimerism. This DNA-based analysis will also be performed on the whole nucleated cell fraction from marrow aspirates. Therapeutic decisions (i.e. DLI) will be made based on the results of sorted T-cell studies of *peripheral blood.* For the purposes of this protocol, *rejection* is defined as the inability to detect or loss of detection of greater than 5% donor T cells (CD3+) as a proportion of the total T cell population, respectively, after nonmyeloablative HCT. Also for the purposes of this protocol, *graft failure* is defined as grade IV thrombocytopenia and neutropenia after day 21 that lasts > 2 weeks and is refractory to growth factor support.

Bone marrow chimerism (unfractionated cells) will be evaluated at day +84 and one year after transplant. In peripheral blood, CD3 chimerism will be evaluated on days +28, +84 and one year after transplant; CD33 chimerism will be evaluated on day +84; CD56 chimerism will be evaluated on day +28. Unless clinically indicated (i.e. poor previous chimerism, immunotherapy, hematopoietic insufficiency etc.), further chimerism studies will not be performed.

I. Continuation of immunosuppression.

In the setting of low donor chimerism, immunosuppression may be continued or reinitiated at full dose so that DLI can be administered on a separate protocol. If there is disease progression in the setting of low donor chimerism, the algorithm for disease progression (below) should be followed. Patients who reject their graft may be eligible for a second allogeneic transplant on other protocols.

J. Discontinuation of immunosuppression.

Immunosuppression should be discontinued as per protocol unless the patient develops GVHD, has falling donor chimerism or has progressive or substantial persistent disease (see below). In the setting of GVHD, CSP and MMF may be continued. GVHD at any time should be treated as per standard practice.

K. Disease progression or persistence and mixed chimerism.

Evidence of substantial persistent disease at day 80 or beyond may be an indication for therapeutic intervention while disease progression, at any time point will always be an indication for therapeutic intervention. Intervention for persistent disease at day 80 or beyond should be discussed with the Principal Investigator and the guideline below for progressive disease should be followed. If the attending physician believes that the patient requires very aggressive therapy for rapidly progressive disease, the case will be presented at the Patient Care Conference (FHCRC patients only). Otherwise, priority should be given to rapid reduction of immunosuppression, option (a) below. Therapeutic options include:

a. Discontinuation of immunosuppression. This should be considered the first therapeutic maneuver. If there is no GVHD, MMF should be stopped and CSP should be tapered over 2 weeks. Bone marrow aspirate and blood chimerism studies will be performed 2 weeks after discontinuation of immunosuppression. If there is no response to withdrawal of immunosuppression, < 20% increase in donor chimerism and there is no GVHD, patients will be considered as treatment failures. DLI will not be offered for disease progression or relapse on this protocol. In this situation, patients may receive further therapy as per institutional protocols for disease relapse or progression after allogeneic HCT. If no GVHD occurs, patients with progressive disease may be offered enrollment in other institutional protocols for DLI treatment. If there is >20% absolute increase in donor chimerism, patients should be observed for additional 2 weeks and chimerism studies then repeated. If there is progressive disease that requires therapy before 4 weeks or progressive disease occurs despite onset of GVHD, patients can be treated off protocol with DLI or be considered for options (b) or (c) below.

b. Intercurrent treatment with chemotherapy or radiation. Conventional chemotherapy or radiation therapy should be considered in the setting of life-threatening progression of malignancy. Patients in this situation would be considered treatment failures. After cytoreductive therapy is completed, chimerism should be evaluated and the administration of DLI off protocol considered.

c. High-dose allogeneic HCT This option should be discussed with the principal investigator. Patients who undergo high-dose allogeneic HCT will be removed from the protocol at that time.

d. CML or Ph (+) ALL patients with Persistent or Increased Minimal Residual Disease: At day +84 or beyond, if the patient has persistent or increased MRD disease, dose-escalation of BCR/ABL tyrosine kinase inhibitor therapy or DLI should be considered

e. CML and PH (+) ALL patients with Relapse and Disease Progression:

See above sections for withdrawal of immunosuppression. If there is no response to withdrawal of immunosuppression and no GVHD has developed, dose escalation of BCR/ABL tyrosine-kinase inhibitor therapy and or DLI should be considered.

L. Assessment of Disease Responses

The initial anti-tumor effect of allogeneic HCT will be evaluated with the intermittent analysis of appropriate tumor markers, if available: Responses will be classified as complete, partial response or no response. Response criteria for MM, NHL, CLL, CML, ALL, AML and MDS to be used in this study are described in Appendix E. Standard response criteria specific to other diseases will be used in assessing disease response for other patients on study.

EVALUATION OF PATIENTS

10.1 Patient Pre-transplant Evaluation for All Diseases

1. History: A complete history with full details of the patient's prior treatment and response.
2. Careful physical exam with documentation of Karnofsky or Lansky score, HCT-CI score and findings related to underlying malignancy.
3. Standard CBC with differential & platelets, comprehensive metabolic panel, magnesium, uric acid, ABO/Rh typing, hepatitis screen, CMV and toxoplasmosis serology, anti-HIV serology, and serum LDH.
4. Pulmonary function tests with corrected DLCO.
5. CXR (PA and LAT).
6. ECHO or MUGA for patients > 50 years of age, or history of cardiac disease or anthracycline exposure.
7. Evaluation and prophylaxis of CNS disease as per local practice guidelines.

Immunophenotyping of the PBSC graft.
Immunophenotyping of the PBSC product will be performed by the Cellular Therapy Laboratory and will include CD34, CD3/4 and CD3/8 cells. The residual specimen will be sent to the Heimfeld lab for phenotypic characterization of cellular subsets. For patients enrolled at external sites, immunophenotyping will be performed at the local site.

Additionally, see the following tables (Tables 4, 5, 6 and 7) for disease specific pre-transplant evaluation

Table 4: Disease-Specific Pre-Transplant Evaluations for ALL and CML

Note: All bone marrow aspirates and biopsies are **unilateral** and must be collected **within 21** days of treatment. See Tables 8 and 10 for post-transplant evaluations and additional lab instructions

Specimen / Test / Imaging	Clinical / Research	Comment
Bone marrow aspirate		
Pathology	Clinical	
Flow Cytometry	Clinical	
Cytogenetics	Clinical	
FISH for clonal abnormalities	Clinical	**If previously abnormal*
PCR for bcr/abl, p.210 breakpoint - **see comment*	Clinical	**CML only*
PCR for bcr/abl, p.190 and p.210 breakpoints - **see comment*	Clinical	**Ph (+) ALL only*
Bone marrow biopsy		
Pathology- **see comment*	Clinical	**CML only*

Table 5: **Disease-Specific <u>Pre-Transplant Evaluations</u> for AML and MDS/MPD**

Note: All bone marrow aspirates and biopsies are **unilateral** and must be collected within **21 days** of treatment. See Tables 8 and 10 for post-transplant evaluations and additional lab instructions

Specimen / Test / Imaging	Clinical / Research	Comment
Bone marrow aspirate		
Pathology	Clinical	
Flow Cytometry	Clinical	
Cytogenetics	Clinical	
FISH for clonal abnormalities	Clinical	**If previously abnormal*
Bone marrow biopsy		
Pathology- **see comment*	Clinical	**MDS/MPD only*

Table 6: **Disease-Specific <u>Pre-Transplant Evaluations</u> for CLL, HL, NHL**

Note: All bone marrow aspirates and biopsies are **bilateral** and must be collected within **30 days** of treatment. See Tables 8 and 10 for post-transplant evaluations and additional lab instructions. If disease status can be determined pre-allo without all specific tests, the tests may be omitted.

Specimen / Test / Imaging	**Clinical / Research**	**Comment**
Bone marrow aspirate		
Pathology	Clinical	
Flow Cytometry- **see comment*	Clinical	**No HL*
Cytogenetics	Clinical	
FISH for clonal abnormalities	Clinical	**If previously abnormal*
PCR for t(11:14) - **see comment*	Clinical	**Mantle Cell NHL only*
PCR for t(14:18) - **see comment*	Clinical	**Follicular NHL only*
Bone marrow biopsy		
Pathology- **see comment*	Clinical	**HL – only if history of BM involvement*
Peripheral Blood		
Quantitative Ig levels	Clinical	
β-2 microglobulin	Clinical	
LDH	Clinical	
ZAP – 70 by flow cytometry- **see comment*	Clinical	**CLL only – for patients not in CR*
Imaging		
CT of chest, abdomen, pelvis (neck if indicated)	Clinical	

Table 7: **Disease-Specific <u>Pre-Transplant Evaluations</u> for MM and Waldenstrom's Macroglobulinemia**

Note: All bone marrow aspirates and biopsies are **bilateral** and must be collected within **30 days** of treatment. See Tables 8 and 10 for post-transplant evaluations and additional lab instructions. If disease status can be determined pre-allo without all specific tests, the tests may be omitted.

Specimen / Test / Imaging	Clinical / Research	Comment
Bone marrow aspirate		
Pathology	Clinical	
Flow Cytometry	Clinical	
Cytogenetics	Clinical	
FISH for clonal abnormalities	Clinical	**If previously abnormal*
Bone marrow biopsy		
Pathology	Clinical	
Peripheral Blood		
SPEP/IFIX	Clinical	
Quantitative Ig levels	Clinical	
β-2 microglobulin	Clinical	
Cryoglobulins, c-reactive protein, serum viscosity - **see comment*	Clinical	**Serum viscosity only for patients with >3gm/dL IgM monoclonal protein or >4gm/dL IgA or IgG protein*
Urine		
UPEP/IFIX	Clinical	
Protein / creatinine clearance	Clinical	
Imaging		
MRI – **see comment*	Clinical	**MM only*
Skeletal survey – **see comment*	Clinical	**MM only*
CT of chest, abdomen, pelvis (neck if indicated) – **see comment*	Clinical	**Waldenstrom's Macroglobulinemia only*

10.2 Patient Post-transplant Evaluation

See Standard Practice Manual for standard treatment guidelines (Allo) during conditioning, post-transplant inpatient admission and during first 100 days after initial hospital discharge. See **Table 8** for disease specific post-transplant evaluation on Day +28, 56, 84, etc; this is a recommended evaluation schedule.

See Standard Practice Manual for Evaluation Guidelines After Departure from FHCRC System.

For patients enrolled at external sites, post-transplant evaluations will be performed per local standard practice. The testing listed in Table 8 are recommended evaluations. All testing will be performed at the local institution.

Guidelines for bone marrow evaluations beyond one year after transplant:

1) Marrow evaluations represent the standard of care for all patients at the one-year LTFU visit after HCT.

2) Subsequent marrow evaluations also represent the standard of care if…
    a. The CBC or platelet count shows any abnormalities
    b. If there is any clinical indication for the procedure, OR
    c. If the most recent marrow evaluation or other testing showed any evidence of persistent malignancy, OR
    d. If the patient has a disease for which a low-dose maintenance treatment would be indicated if disease were discovered after a previous evaluation with no evidence of malignant cells.

Table 8: Post-Transplant Evaluation
This is a recommended evaluation schedule.
See Tables 4 - 7 for pre-transplant evaluations. Additional lab instructions in Table 9.

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
Ph (-) ALL	**BM aspirate*** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for clonal abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical		x						
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
Ph (+) ALL	**BM aspirate*** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical		x	x	x	x	x	x	x
	FISH for bcr/abl and other clonal abnormalities	Clinical		x	x	x	x	x	x	x
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	PCR for bcr-abl, p.190 and p.210 breakpoints	Clinical	* p.190 and p.210 only if present in pre-transplant marrow	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	GVHD evaluation	Clinical	See text for details			x				

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Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
AML	**BM aspirate*** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for clonal abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
MDS/ MPD	**BM aspirate** **see biopsy* ** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for clonal abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	BM biopsy									
	Pathology	Clinical	*For pts. with evidence or history of myelofibrosis	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
CML	**BM aspirate** **see biopsy* ** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical		x	x	x	x	x	x	x
	FISH for bcr-abl and other clonal abnormalities	Clinical		x	x	x	x	x	x	x
	BM biopsy									
	Pathology	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	PCR for bcr-abl, and p.210 breakpoint	Clinical	*p.190 and p.210 only if present in pre-transplant marrow	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
CLL	**BM aspirate** **see biopsy* ** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for clonal abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	BM biopsy									
	Pathology	Clinical				x	x	x	x	x
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	Flow cytometry	Clinical	* If peripheral blood involvement pre-transplant AND bone marrow not done	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Quantitative Ig levels	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment	*See comment	*See comment
	LDH	Clinical			x	x	x	x	x	x
	Imaging									
	CT chest, abdomen, pelvis (neck if indicated)	Clinical	*Day 56 only if abnormal pre-transplant		*See comment	x	x	x	x	x
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
HL - No history of BM involvement	**BM aspirate*** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical				x		x		
	Cytogenetics	Clinical	*If abnormal pre-transplant			*See comment		*See comment		
	FISH for clonal abnormalities	Clinical	*If abnormal pre-transplant			*See comment		*See comment		
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	LDH	Clinical			x	x	x	x	x	x
	Imaging									
	CT chest, abdomen, pelvis (neck if indicated)	Clinical	*Day 56 only if abnormal pre-transplant		*See comment	x	x	x	x	x
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
HL - History of BM involvement	**BM aspirate** **see biopsy* ** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for clonal abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	BM biopsy									
	Pathology	Clinical				x	x	x	x	x
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	LDH	Clinical			x	x	x	x	x	x
	Imaging									
	CT chest, abdomen, pelvis (neck if indicated)	Clinical	*Day 56 only if abnormal pre-transplant		*See comment	x	x	x	x	x
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
NHL – No History of BM involvement **see separate section for additional PCR on Mantle Cell and Follicular NHLs in suspected CR*	**BM aspirate *** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical				x		x		
	Flow cytometry	Clinical				x		x		
	Cytogenetics	Clinical	*If abnormal pre-transplant			*See comment		*See comment		
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	Flow cytometry	Clinical	* If peripheral blood involvement pre-transplant, if bone marrow not obtained	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	β-2 microglobulin	Clinical				x				
	LDH	Clinical				x	x	x	x	x
	Imaging									
	CT chest, abdomen, pelvis (neck if indicated)	Clinical	*Day 56 only if abnormal pre-transplant		*See comment	x	x	x	x	x
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
NHL– History of BM involvement **see separate section for additional PCR on Mantle Cell and Follicular NHLs in suspected CR*	**BM aspirate** **see biopsy* ** ** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for clonal abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	BM biopsy									
	Pathology	Clinical				x	x	x	x	x
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	Flow cytometry	Clinical	* If peripheral blood involvement pre-transplant, if bone marrow not obtained	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	β-2 microglobulin	Clinical				x		x		
	LDH	Clinical			x	x	x	x	x	x
	Imaging									
	CT chest, abdomen, pelvis (neck if indicated)	Clinical	*Day 56 only if abnormal pre-transplant		*See comment	x	x	x	x	x
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
Mantle Cell NHL *in suspected CR*	**BM aspirate** **in addition to complete NHL restaging* ** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	PCR for t(11:14)	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood **in addition to complete NHL restaging*									
	PCR for t(11:14)	Clinical	*If abnormal pre-transplant, if bone marrow not obtained	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
Follicular Cell NHL *in suspected CR*	**BM aspirate** **in addition to complete NHL restaging* ** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	PCR for t(14:18)	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood **in addition to complete NHL restaging*									
	PCR for t(14:18)	Clinical	*If abnormal pre-transplant, if bone marrow not obtained	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
MM *Omit SPEP/IFIX and UPEP/IFIX for non-secretory MM*	**BM aspirate***If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for chrom. 13 (and other clonal) abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	SPEP and IFIX	Clinical				x	x	x	x	x
	Quantitative Ig levels	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment	*See comment	*See comment
	β-2 microglobulin	Clinical				x	x	x	x	x
	Cryoglobulins, C-reactive protein, viscosity	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment		*See comment
	Urine									
	Protein/creatinine clearance	Clinical				x	x	x	x	x
	UPEP and IFIX	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment	*See comment	*See comment
	Imaging									
	Complete skeletal survey	Clinical						x		x
	Skeletal MRI	Clinical						x		x
	GVHD evaluation	Clinical	See text for details			x				

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
Waldenstrom's Macro-globulinemia *Omit SPEP/IFIX and UPEP/IFIX for non-secretory Waldenstrom's Macro-globulinemia*	**BM aspirate*** If CR documented at one year, and there is recovery of normal blood counts, bone marrow after one year may be obtained based on clinical judgment									
	Chimerism	Clinical				x		x		
	Pathology	Clinical		x	x	x	x	x	x	x
	Flow cytometry	Clinical		x	x	x	x	x	x	x
	Cytogenetics	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	FISH for chrom. 13 (and other clonal) abnormalities	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	Peripheral blood									
	Chimerism (CD3+)	Clinical	*Days 56 and 180 only if <50% on day 28	x	*See comment	x	*See comment	x		
	Chimerism (CD33+)	Clinical				x				
	Chimerism (NK CD56+)	Clinical	Optional for outside institutions	x						
	SPEP and IFIX	Clinical				x	x	x	x	x
	Quantitative Ig levels	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment	*See comment	*See comment
	β-2 microglobulin	Clinical					x	x	x	x
	Cryoglobulins, C-reactive protein, viscosity	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment		*See comment
	Urine									
	Protein/ creatinine clearance	Clinical				x	x	x	x	x
	UPEP and IFIX	Clinical	*If abnormal pre-transplant			*See comment	*See comment	*See comment	*See comment	*See comment
	Imaging									
	CT chest, abdomen, pelvis (neck if indicated)	Clinical	*Day 56 only if abnormal pre-transplant		*See comment	x	x	x	x	x
	GVHD evaluation	Clinical	See text for details			x				

Table 9: Additional Lab Instructions (for patients enrolled at FHCRC)

Note: All bone marrow tests are done on aspirate unless specifically identified as biopsy. All instructions apply to both pre- and post-transplant evaluations unless specifically identified otherwise. Volumes represent desired amounts.

Specimen / Test	Type	Instructions	Lab Name	Contact Information
Bone marrow				
Chimerism	Clinical	1-3mL bone marrow in green-top tube	Clinical Immunogenetics Lab	Seattle Cancer Care Alliance (206) 606-7700
Pathology (*aspirate*)	Clinical	2mL bone marrow in EDTA formalin	SCCA Pathology Lab	Seattle Cancer Care Alliance (206) 606-1355
Pathology (*biopsy*)	Clinical	1cm bone marrow in formalin **OR** mounted in paraffin	SCCA Pathology Lab	Seattle Cancer Care Alliance (206) 606-1355
Flow Cytometry	Clinical	2mL bone marrow in green-top tube	UW Hematopathology Lab	Seattle Cancer Care Alliance (206) 606-7060
Cytogenetics	Clinical	3mL bone marrow in green-top tube	SCCA Cytogenetics Lab	Seattle Cancer Care Alliance (206) 606-1390
FISH	Clinical	2mL bone marrow in green-top tube	SCCA Cytogenetics Lab	Seattle Cancer Care Alliance (206) 606-1390
PCR for bcr-abl and p190 and/or p210	Clinical	3mL bone marrow in lavender-top tube Label "protocol 2546"	UW Molecular Hematopathology Lab	Mailstop G7-800 825 Eastlake Ave, East Seattle, WA 98109 (206) 606-7060
PCR t(11:14) or t(14:18)	Clinical	2mL bone marrow in lavender-top tube	UW Molecular Hematopathology Lab	Mailstop G7-800 825 Eastlake Ave, East Seattle, WA 98109 (206) 606-7060
Peripheral blood				
Chimerism (CD3+), (CD33+) NK(CD56+)	Clinical	10mL blood in green-top tube for Flow sorting, then to CIL	UW Hematopathology Lab, routed to Clinical Immunogenetics Lab	Mailstop G7-800 825 Eastlake Ave, East Seattle, WA 98109 (206) 606-7060
Flow Cytometry	Clinical	10mL blood in green-top tube	UW Hematopathology Lab	Seattle Cancer Care Alliance (206) 606-7060
SPEP/IFIX	Clinical	3mL blood in red-top tube	UW Department of Laboratory Medicine	University of Washington (800) 713-5198
Quantitative Ig Levels	Clinical	3mL blood in red-top tube	SCCA Alliance Lab	Seattle Cancer Care Alliance (206) 606-2057
β-2 Microglobulin	Clinical	3mL blood in red-top tube	UW Department of Laboratory Medicine	University of Washington (800) 713-5198
LDH	Clinical	3mL blood in red-top tube	SCCA Alliance Lab	Seattle Cancer Care Alliance (206) 606-2057
PCR for bcr-abl and p190 and/or p210	Clinical	7mL blood in lavender-top tube Label "protocol 2546"	UW Molecular Hematopathology Lab	Mailstop G7-800 825 Eastlake Ave, East Seattle, WA 98109 (206) 606-7060
PCR for t(11:14) or t(14:18)	Clinical	5mL blood in lavender-top tube	UW Molecular Hematopathology Lab	Mailstop G7-800 825 Eastlake Ave, East Seattle, WA 98109 (206) 606-7060
ZAP – 70 by Flow cytometry (*pre-transplant only*)	Clinical	5mL blood in green-top tube	UW Hematopathology Lab	Mailstop G7-800 825 Eastlake Ave, East Seattle, WA 98109 (206) 606-7060

EVALUATION OF DONORS

See Standard Practice Manual for standard Evaluation Guidelines of allogeneic PBSC donors. Evaluation of donors at external sites will be per the local standard practice.

11.1 Safety Evaluations

Laboratory parameter monitoring: *Rhabdomyolysis* (defined as a creatine phosphokinase [CPK] value > 10fold the upper limit of normal) and *hepatocellular injury* are infrequent yet potentially serious complications of statin treatment. Therefore, serum levels of CPK and transaminases will be assessed before initiation of atorvastatin treatment (baseline) and at its completion (first day of leukapheresis).

Muscular symptom monitoring: Because rare cases of rhabdomyolysis have been reported with atorvastatin (approximately 1 in 1,000 patients), donors will be instructed to report any new muscle symptoms (i.e. myalgias, tenderness, weakness) while taking atorvastatin. Taking into account that G-CSF (Neupogen™) frequently causes musculoskeletal symptoms, any symptoms temporally related to atorvastatin treatment considered significant according to the medical team's assessment will be evaluated at the attending physician's discretion.

Liver dysfunction monitoring: Persistent elevations in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials and, in most cases, were not associated with clinical symptoms. Transaminase elevations related to atorvastatin treatment are usually reversible after discontinuation of the drug and measurements of serum transaminase levels are generally not recommended until completion of 12 weeks of atorvastatin treatment. As outlined under "Laboratory parameter monitoring", serum levels of transaminases will be assessed before initiation of atorvastatin treatment (baseline) and at its completion (first day of leukapheresis). If clinically indicated, additional measurements of serum transaminase levels may be performed at the attending physician's discretion.

Monitoring for other symptoms: Any new and unexplained significant signs or symptoms occurring in statin-treated donors should be evaluated according to the judgment of the attending physician. Approximately one week after initiation of statin therapy, at the time of PBSC collection and one week after donation and discharge from the center, the donor will be contacted by study staff (at the local transplant center or by telephone) to follow up on potential adverse effects that may require further evaluation. At the same time, the donor will also be asked about his/her compliance with the prescribed atorvastatin medication.

If the donor develops clinical signs or symptoms deemed serious and at least possibly related to statin treatment, the attending physician, in consultation with the Principal Investigator, will decide whether atorvastatin treatment should be discontinued. In this case, the donor will be provided with an appropriate follow-up plan, which will be formulated by the attending physician and the PI.

11.2 Donor Statin Compliance

Donor compliance with taking atorvastatin will be monitored at the time of each donor contact specified above in Section 11.1.

TOXICITIES AND COMPLICATIONS

For the purposes of this protocol, toxicity will be graded using the modified NCI common toxicity scale version 4.0.

12.1 Atorvastatin

- **Skeletal Muscle**

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin (<1 in 1,000 patients). A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Patients with renal impairment therefore merit closer monitoring for skeletal muscle effects. Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CPK values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

- **Liver Dysfunction**

Atorvastatin has been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the ULN occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively. One patient in clinical trials developed jaundice. Increases in LFTs in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is generally recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin.

- **Endocrine Function**

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

- **CNS Toxicity**

Brain hemorrhage, optic nerve vacuolation and degeneration, and CNS vascular lesions were seen after long-term treatment of normal dogs with atorvastatin or similar drugs in this class at doses that produced plasma drug levels 6-30 times higher than those attainable in humans taking the highest recommended statin dose.

- **Additional Adverse Reactions**

Clinical Trial Adverse Experiences: In the Lipitor™-placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin and 9.5% of the patients on placebo discontinued therapy due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%). The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%). **Table 13** summarizes the frequency of clinical adverse reactions from 17 placebo-controlled trials, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin (n=8755).

Table 13. Clinical adverse reactions occurring in > 2% in patients treated with any dose of atorvastatin (Lipitor™) and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse Reaction > 2% in any dose greater than placebo

Other adverse reactions reported in placebo-controlled studies include:
Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, flatulence, hepatitis, cholestasis; *Musculo-skeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, LFT abnormality, blood alkaline phosphatase increase, serum CPK increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system:* epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

12.2 GVHD

Acute and chronic GVHD are well-recognized complications of allogeneic hematopoietic cell transplantation. GVHD will be assessed according to criteria summarized in Appendices B, C and D. Recommended primary systemic treatment for acute GVHD will be corticosteroids. Other systemic immunosuppressive medications may be used at the discretion of the attending physician.

12.3 Total Body Irradiation (TBI)

TBI will be given in one 200 cGy or up to 400 cGy fraction (per institutional guidelines) from linear accelerator at a rate of 6 - 7 cGy/min. Dosimetry calculations are performed by the radiation therapist. At the dose used, side effects are not expected. Nevertheless, there may be fever, alopecia, parotitis, diarrhea, reversible skin pigmentation, mucositis and late effects including cataract formation, growth retardation, pulmonary damage, carcinogenesis, and sterilization.

12.4 Cyclosporine (CSP)

See section 9.2. for information about administration and dose adjustment. Side effects are generally reversible, and may include renal insufficiency, hypomagnesemia, paresthesias, tremor, seizures, visual disturbances, paresis, disorientation, depression, confusion, somnolence, coma, nausea, hypertension, hemolytic-uremic syndrome, hyperglycemia, gynecomastia, and hypertrichosis

12.5 Mycophenolate Mofetil (MMF)

See section 9.2. for information about administration and dosage adjustments.

Precautions: MMF has been studied extensively among patients after nonmyeloablative HCT. Previous clinical studies in patients after allografting suggest that the principal adverse reactions associated with the administration of MMF include nausea, vomiting, neutropenia, diarrhea. In the setting of marrow transplantation, several etiologic factors may contribute to alterations in gastrointestinal and hematologic parameters. MMF has an increased incidence of digestive system adverse events, including GI tract ulceration, and hemorrhage (3% of patients receiving MMF). GI tract perforations have rarely been observed. Most patients in these studies were also on other drugs known to be associated with these complications. Up to 2% of patients receiving MMF for prevention of rejection developed severe neutropenia (ANC <500). The development of neutropenia may be related to MMF itself, concomitant medications, viral infections or some combination of these causes. MMF dose adjustments will be made if clinically indicated if in the opinion of the attending physician, no other cause is thought to be responsible for the abnormality. These adjustments should be discussed with the principal investigator and documented in the medical records and the clinical reporting form (CRF).

12.6 Fludarabine

The dose of fludarabine used in this protocol is nonmyeloablative, but does cause significant immunosuppression. Fludarabine can lower the white blood cell count, in particular the CD4+ T-cells. The immunosuppression observed with the use of fludarabine increases the risk of infection, which can be life threatening.

12.7 Myelosuppression

Grade IV myelosuppression will be defined as a decrease in ANC to ≤500/μL and/or platelet count to ≤ 20,000/μL. If myelosuppression occurs, a bone marrow aspirate and biopsy should be considered to exclude disease progression. Samples should be sent for chimerism analysis. Myelosuppression may occur in this patient population for a number of reasons such as direct toxic effect of drugs (MMF, ganciclovir etc.), rejection, relapse or after DLI.

ADVERSE EVENT MONITORING

13.1 Institutional Policy and Definitions

- **Policy**

The following guidelines are the minimum Cancer Consortium IRB adverse event (AE) reporting guidelines.

In accordance with institutional policy, all serious adverse events (SAEs) which in the opinion of the principal investigator are unexpected and related or possibly related to the research and serious or suggest that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized must be reported to the IRB within 10 calendar days of learning of the problem. **Since only stem cell donors and not recipients will be treated with atorvastatin according to this study, monitoring of non-serious AEs will focus on the donors**. **Non-serious AEs occurring in the patient will not be collected.** The Cancer Consortium Expedited Reporting Form for Unanticipated Problems or Noncompliance should be completed for all adverse events that meet the expedited reporting requirements. The form should be sent to the Institutional Review Office (IRO) within 10 calendar days of learning of the problem.

SAE Policy and Reporting at External Sites: For SAEs that occur in patients enrolled at external sites, reporting to the local IRB will be per the local institutional policy. This will apply to expedited and annual reporting. It will be the responsibility of the external site to submit to FHCRC an SAE report for all SAEs that occur in patients and donors. These reports must be sent to FHCRC within 10 days of learning of the event.

Please see **Appendix F** for definitions of adverse events, serious adverse events (SAE) and serious and unexpected events as well as mechanisms for reporting these events

13.2 Adverse Events to be Monitored in This Study

- **Serious Adverse Events**

- SAEs: All events occurring in donors and recipients that meet the definition of an SAE will be recorded and reported to the IRB, regardless of whether they are related or unrelated to the protocol intervention or are expected or unexpected. SAEs observed in donors or recipients that are deemed related or possibly related and unexpected to the research will be reported to the IRB in an expedited fashion (within 10 calendar days of learning of the problem). All other SAEs will be reported to the IRB at the time of annual protocol renewal.

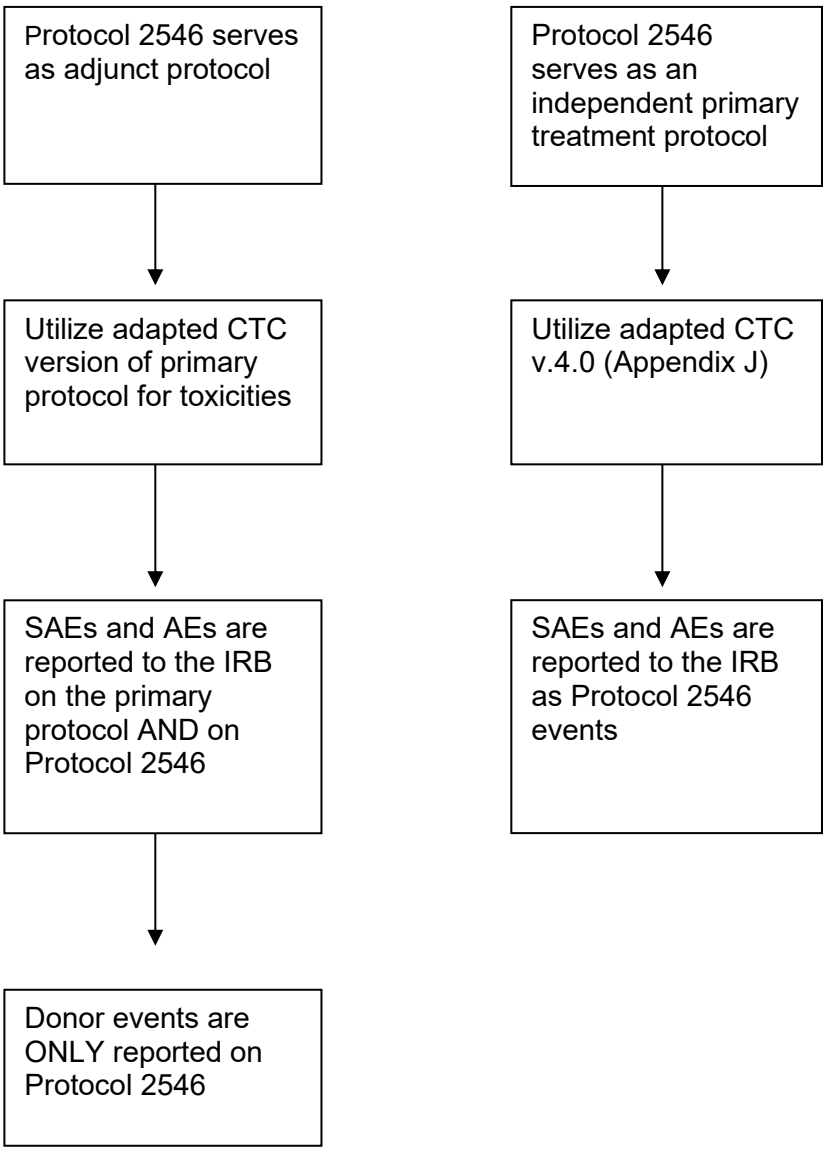
- **Adverse Events Related to Administration of Atorvastatin**

- Select toxicities will be collected using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0 (Appendix I)
- Since the primary research intervention in this study is the administration of atorvastatin to PBSC donors before stem cell collection (for prevention of severe acute GVHD in recipients), reporting of AEs that are *not serious* will focus on atorvastatin-related events in donors. Although highly unlikely, the potential negative impact of donor statin treatment on recipient outcomes will be captured through no-harm endpoints that trigger mandatory DSMB review as further outlined in 17.3.
- Donors will be assessed for the following events:
    - Musculoskeletal and connective tissue disorders: grade 2-5
    - Hepatobiliary disorders: grade 2-5
    - Other unexpected events thought related to the use of atorvastatin; grade 2-5

In cases where the NCI criteria do not apply, intensity will be defined as:

- Mild: awareness of symptom or sign, but easily tolerated
- Moderate: discomfort is enough to cause interference with normal activities
- Severe: inability to perform normal daily activities
- Life threatening: immediate risk of death from the reaction as it occurred

Figure 3: SAE reporting for patients on Protocol 2546 as an independent primary treatment Protocol or as an adjunct:



13.3 Duration of Adverse Event and Unanticipated Problem Monitoring and Recording

Donor: SAEs and select AEs (see section 13.2) will be monitored and recorded from the time the donor starts atorvastatin therapy through 7 days after the discontinuation of the medication.

Recipient: SAEs (life-threatening or fatal)

- **For 2546 as an adjunct to treatment plan or primary protocol**, SAEs will be monitored and recorded from the time the recipient starts conditioning therapy through day 100 or discharge from the center, whichever occurs earlier.

- **For 2546 as an adjunct to a nonmyeloblative investigational protocol**, follow reporting guidelines of nonmyeloblative investigational protocol.

OUTCOMES TO BE ASSESSED

14.1 Proportion of Donors who Discontinue Atorvastatin Because of Toxicity

During treatment with atorvastatin, donors will be evaluated for adverse effects that would mandate discontinuation of the drug. Data pertaining to atorvastatin toxicity including those mandating discontinuation of the drug will be collected per Section 13.

14.2 Acute GVHD

All patients will be evaluated for GVHD. It is strongly recommended, when possible, that biopsies be taken for histological confirmation of GVHD. The final peak grade of GVHD will be determined retrospectively by Dr. Paul Martin. Data pertaining to the diagnosis and treatment of acute GVHD will be collected though day +100 post-transplant.

14.3 Chronic GVHD

Patients will be evaluated for chronic GVHD as described in the NIH consensus project guidelines. Graft failure, recurrent malignancy and death without GVHD are considered to be competing risks for GVHD.

14.4 Recurrent Malignancy

Recurrent malignancy will be defined by hematologic criteria. Recurrent malignancy will also be defined as any unplanned medical intervention designed to prevent progression of malignant disease in patients who have molecular, cytogenetic or flow-cytometric evidence of malignant cells after transplantation.

14.5 Non-relapse Mortality (NRM)

NRM is defined as death in the absence of recurrent or progressive malignancy after HCT.

14.6 Overall Survival (OS)

Survival without death (OS) will be determined and presented as Kaplan-Meier estimates at 1 year post-transplant.

14.7 Proportion of Patients Requiring Secondary Systemic Immunosuppressive Treatment

The need for additional systemic immunosuppressive treatment with agents other than those used for prophylaxis and initial therapy, the reason for their administration (acute GVHD, chronic GVHD, or other reasons) will be determined.

DATA AND SAFETY MONITORING PLAN

15.1 Principal Investigator

- **Responsibilities**
  - Coordinating development of the protocol as well as its subsequent amendments.
  - Securing initial IRB and NHLBI approval of the protocol
  - Securing IRB approval of protocol amendments.
  - Reviewing and adjudicating whether SAEs are unexpected and related to administration of atorvastatin to donors before stem cell collection.
  - Securing renewal of IRB approval at annual intervals.

- **Oversight Mechanisms**

To identify trends pertinent to patient or donor safety, the Principal Investigator will meet with the research nurse and other key investigators to review enrollment, SAEs and AEs in the donors that might be related to administration of atorvastatin. Patient data (day 100 NRM and recurrent malignancy) will also be reviewed.

15.2 Data Safety Monitoring Board (DSMB)

- **Role of the DSMB**

This study will be monitored by a DSMB. The primary role of the DSMB will be to monitor protocol specific AEs and SAEs in the donors , even though occurrence of SAEs in donors probably or likely related to short-term atorvastatin treatment is considered highly unlikely. The DSMB will monitor acute GVHD, relapse, non-relapse mortality and overall survival in the patients.

- **DSMB Membership**

Membership will consist of one statistician and two senior physicians who are familiar with HCT. To avoid any conflict of interest, DSMB members are required to have no study involvement. Potential conflicts of interest will be reviewed by the IRB at the time of initial DSMB appointment.

- **Operations and Responsibilities of the DSMB**

The DSMB will meet after the first cohort of 13 donors have completed the stem cell donation process. Subsequent meetings will be held at 12-month intervals. At each meeting the DSMB will review data related to donor and patient safety. It is anticipated that the donor safety monitoring will include a review of all protocol-specific adverse events and AEs and SAEs. Even though there has been no indication based on large retrospective analyses that donor statin

treatment may negatively affect recipients' outcomes [2], rates of recurrent malignancy and day-100 mortality in recipients will be carefully monitored and considered during DSMB review.

Based on the information available at each of these meetings, the DSMB is charged with deciding whether a) no action is required, b) the protocol should be modified, c) further enrollment should be suspended pending additional review, or d) the protocol should be closed.

The DSMB will keep minutes of its meetings and provide its findings to the Principal Investigator within 10 working days. An exception to this time requirement will occur if the DSMB recommends study termination, suspension of enrollment or a protocol modification that significantly affects donor or patient safety. In these cases, the DSMB will be expected to provide their recommendations to the Principal Investigator within 24 hours. Ad hoc meeting or discussion with the DSMB will be arranged as deemed necessary by the protocol PI.

- **Reporting Data to the DSMB**

The Principal Investigator will be responsible for providing the DSMB with summary data sufficient to meet its responsibilities.

15.3 Trial Monitoring

Trial monitoring is provided in accordance with the FHCRC/University of Washington (UW) Cancer Consortium Data and Safety Monitoring Plan (DSMP). Under the provisions of the DSMP, the Cancer Consortium Clinical Trial Support Office provides monitoring for quality process and compliance by qualified monitors unaffiliated with the conduct of the study. Monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of the previous visit. The scope of monitoring is specified in the DSMP http://www.cancerconsortium.org/rto/prr/

Per FHCRC IRB Policy 1.9, all confirmed serious or continuing noncompliance with federal laws relating to research involving human subjects, the FHCRC human subject protection program (HRPP) or the requirements of the IRB will be reported promptly to either the IRO Director or other entities cited in the policy.

DATA MANAGEMENT AND PROTECTION OF CONFIDENTIALITY

Clinical Statistics maintains a subject database at FHCRC to allow storage and retrieval of local subject data collected from a wide variety of sources. The investigator will ensure that data collected conform to all established guidelines for coding, collection, key entry and verification. Each subject is assigned a unique patient number to assure subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the Consortium institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents. Subject research files are scanned and stored securely in an optical web library (OWL). OWL records are maintained by the FHCRC data abstraction staff. Access is restricted to personnel authorized by the Division of Clinical Research.

STATISTICAL CONSIDERATIONS

17.1 Primary Endpoint and Sample Size

The primary endpoint of this study is the proportion of patients who develop grade 3-4 acute GVHD after transplantation. The cumulative incidence of this endpoint in patients prepared with nonmyeloablative conditioning regimens after HCT from HLA-matched related donors, and with CSP-based immunosuppression is approximately 9%. A reduction in the cumulative incidence of acute GVHD from 9% to <2% would represent a reasonable goal after nonmyeloablative HCT and constitute study success. Patients with GVHD symptoms that are equivocal with respect to assigning severity and grade will be reviewed by at least two GVHD attendings to arrive at consensus grading. Based on a hypothetical total of 100 patients evaluated, **Table 14** illustrates the decreasing confidence that a true rate of grade 3-4 acute GVHD of <9% exists corresponding to increasing numbers of patients in whom grade 3-4 acute GVHD is observed. Having 90% confidence that a true grade 3-4 GVHD rate of <9% exists appears sufficient to define success of this study; therefore, donor/patient pairs would be enrolled until the 6th patient develops grade 3-4 acute GVHD. If a 6th patient develops grade 3-4 acute GVHD, the study would be closed for lack of demonstrable efficacy. Patients with GVHD symptoms that are equivocal with respect to assigning severity and grade will be reviewed by at least two GVHD attendings to arrive at consensus grading.

Table 14. Confidence of that a true rate of grade 3-4 acute GVHD of <9% exists as a function of increasing numbers of patients in whom grade 3-4 acute GVHD is observed.

N cases GVHD	Confidence < 9%	Power[1] if True = 4%	Power[1] if True = 2%
0	>99	2	13
1	>99	9	40
2	>99	23	68
3	98	43	86
4	95	63	95
5	90	79	98
6	81	89	>99

[1]Probability of observing indicated number of cases or fewer among a total number of **100** patients

Stopping rules will be imposed for:

- Grade 3-4 acute GVHD in 6/100 patients

Patients who have to discontinue CSP because of toxicity before onset of GVHD and who subsequently develop grade 3-4 acute GVHD will not be considered for assessment of efficacy. As long as <6 patients have developed grade 3-4 acute GVHD, the study would continue to enroll up to a maximum of 100 donor/recipient pairs.

17.2 Secondary Endpoints

- **Acute and chronic GVHD**

Grades II-IV and II-IV acute GVHD and chronic GVHD will be assessed with the use of cumulative incidence plots.

- **Non-relapse Mortality**

Non-relapse mortality will be assessed with the use of cumulative incidence plots. This secondary endpoint will be characterized and presented as a cumulative incidence at day 100 and at 1 year after HCT.

- **Recurrent or progressive Malignancy**

Recurrent or progressive malignancy will be assessed with the use of cumulative incidence plots.

- **Overall survival**

Disease-free survival and overall survival will be evaluated as Kaplan-Meier estimates at 1 year after HCT.

- **Duration of Systemic Immunosuppressive Treatment**

Primary and secondary treatment of acute GVHD and withdrawal of systemic immunosuppressive treatment will be assessed with the use of cumulative incidence plots.

- **Discontinuation of Atorvastatin Therapy**

The number of donors who prematurely discontinue atorvastatin therapy and the reasons for discontinuation will be described.

17.3 Mandatory *Ad Hoc* DSMB Review

This protocol is designed to evaluate GVHD-protective effects associated with donor statin treatment as a novel approach to immunosuppression after nonmyeloablative HCT from HLA-matched related donors. Although deemed extremely unlikely, an *ad hoc* DSMB review will be convened if interim results raise concerns about donor safety, particularly with respect to muscle and hepatic toxicity. In large studies using atorvastatin for long-term treatment of patients with hyperlipidemia, SAEs were rare (<1%), did not increase across the 10 mg/day to 80 mg/day dose-range and seldom led to study withdrawal. Based on this review, the DSMB will make a determination as to whether the protocol should be closed to accrual.

Even though there has been no indication based on large retrospective analyses that donor statin treatment may negatively affect recipients' outcomes [2], rates of recurrent malignancy and day-100 mortality in recipients will be carefully monitored and considered during DSMB review. In the unlikely event that there was evidence suggesting donor statin treatment causes harm in recipients, the DSMB may recommend modification or closure of the study.

17.4 Projected Ethnic and Gender Distribution

Table 15: ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex / Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	2	3
Not Hispanic or Latino	41	56	97
Ethnic Category Total of All Subjects*	42	58	100
Racial Categories			
American Indian / Alaska Native	1	1	2
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	39	54	93
Racial Categories: Total of All Subjects*	42	58	100

TERMINATION OF STUDY

Participants may withdraw from this study at any time at their discretion. Participants may also be removed from this protocol if they develop any untoward side effects from the study medications. In addition, stopping rules are in place for lack of efficacy and a DSMB will evaluate issues related to excessive toxicity observed in patients or donors thought to be related to atorvastatin.

The PI may terminate the study at any time. The IRB and the United States Food and Drug Administration also have the authority to terminate the study should it be deemed necessary.

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TABLE OF APPENDICES

Appendix A: Lipitor (atorvastatin) Product label

http://labeling.pfizer.com/ShowLabeling.aspx?id=587

APPENDIX B:

CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD)

Chronic GVHD in allogeneic transplant recipients resembles autoimmune disorders such as scleroderma, Sjogren syndrome, primary biliary cirrhosis, lichen planus, wasting syndrome, bronchiolitis obliterans among others manifestations (see below). Approximately 50% of patients will develop this complication within 6 months after the transplant despite continued treatment with immunosuppressive medications. Close monitoring is recommended during the first 2 years after allogeneic stem cell transplantation so that appropriate treatment can be instituted promptly in patients who develop chronic GVHD. Debilitation, joint contractures and profound immunosuppression resulting in recurrent bacterial infections are prominent characteristics of untreated chronic GVHD.

A. Classification of Chronic GVHD

The purpose of this classification is to identify patients with cGVHD who need long-term systemic immunosuppression according to clinical and laboratory findings and risk factors at the time of initial diagnosis.

1. **Chronic GVHD not requiring systemic treatment: mild abnormalities involving a single site, with platelet count >100,000 and no steroid treatment at the onset of chronic GVHD**
   a) Oral abnormalities consistent with cGVHD, a positive skin or lip biopsy, and no other manifestations of cGVHD
   b) Mild liver test abnormalities (alkaline phosphatase ≤2 x upper limit of normal, AST or ALT ≤3 x upper limit of normal and total bilirubin ≤1.6) with positive skin or lip biopsy, and no other manifestations of cGVHD
   c) Less than 6 papulosquamous plaques, macular-papular or lichenoid rash involving <20% of body surface area (BSA), dyspigmentation involving <20% BSA, or erythema involving <50% BSA, positive skin biopsy, and no other manifestations of cGVHD
   d) Ocular sicca (Schirmer's test ≤5mm with no more than minimal ocular symptoms), positive skin or lip biopsy, and no other manifestations of cGVHD
   e) Vaginal or vulvar abnormalities with positive biopsy, and no other manifestations of cGVHD

2. **Chronic GVHD requiring systemic treatment: more severe abnormalities or involvement of multiple sites, or platelet count <100,000, or steroid treatment at the onset of chronic GVHD**
   a) Involvement of two or more organs with symptoms or signs of cGVHD, with biopsy documentation of cGVHD in any organ
   b) ≥15% base line body weight loss not due to other causes, with biopsy documentation of cGVHD in any organ
   c) Skin involvement more extensive than defined for clinical limited cGVHD, confirmed by biopsy
   d) Scleroderma or morphea
   e) Onycholysis or onychodystrophy thought to represent cGVHD, with documentation of cGVHD in any organ
   f) Decreased range of motion in wrist or ankle extension due to fasciitis caused by cGVHD
   g) Contractures thought to represent cGVHD
   h) Oral involvement with functional impairment, refractory to topical treatment
   i) Vaginal involvement with functional impairment, refractory to topical treatment
   j) Bronchiolitis obliterans not due to other causes
   k) Positive liver biopsy; or abnormal liver function tests not due to other causes with alkaline phosphatase >2 x upper limit of normal, AST or ALT >3 x upper limit of normal, or total bilirubin >1.6, and documentation of cGVHD in any organ
   l) Positive upper or lower GI biopsy

m) Fasciitis or serositis thought to represent cGVHD and not due to other causes

B. Physical manifestations of Chronic GVHD
Manifestations that are distinctive for chronic GVHD can begin before day 100 after the transplant, and manifestations that are typical of acute GVHD can persist long after day 100. For this reason, the differential diagnosis between acute and chronic GVHD cannot be made solely according to the time interval from transplant. The diagnosis of chronic GVHD requires at least one manifestation that is distinctive for chronic GVHD (*identified by italic print below*) as opposed to acute GVHD. In all cases, infection and others causes must be ruled out in the differential diagnosis of chronic GVHD.

Karnofsky or Lansky Clinical Performance scores <60%, ≥15% weight loss, and recurrent infections are usually signs of clinical extensive chronic GVHD. Abnormalities that could indicate chronic GVHD are categorized by organ system are listed below (*italic print identifies manifestation more distinct of chronic GVHD):*

Skin	Erythema, dryness, pruritis, macular-papular or urticarial rash, *pigmentary changes (i.e., hyperpigmentation, vitiligo), mottling, papulosquamous or lichenoid plaques, hyperkeratosis, exfoliation (ichthyosis), nodules, scleroderma, morphea (one or several circumscribed, indurated and shiny lesions)*. The extent of skin involvement and the skin thickness score for patients with scleroderma needs to be recorded at the time of diagnosis, when changes in treatment are made and when assessing treatment response. Medical photos are also useful for assessing the extent of skin involvement and response to treatment.
Nails	**B. Ridging, onychodystrophy, onycholysis**
Hair	*Premature graying (scalp hair, eyelashes, eyebrows), thinning scalp hair, alopecia, decreased body hair*
Mouth	Dryness, burning, gingivitis, mucositis, striae, *dryness, atrophy, erythema, lichenoid changes, ulcers, labial atrophy or pigmentary changes, tightness around the mouth, sensitivity to acidic, strong flavors, heat or cold, tooth decay*
Eyes	*Dryness, burning, blurring, gritty eyes, photophobia, pain*
Vagina/vulva	*Dryness, dyspareunia, stricture or stenosis, erythema, atrophy or lichenoid changes not induced by ovarian failure or other causes*
Liver	Jaundice and elevated liver function tests not due to other causes (see laboratory tests)
Lung	*Bronchiolitis obliterans (see diagnostic indicators), cough, wheezing, dyspnea on exertion, history of recurrent bronchitis or sinusitis*
GI	Anorexia, nausea, vomiting, diarrhea, *malabsorption, dysphagia, odynophagia*
Myofascial	*Stiffness and tightness with restriction of movement, occasionally with swelling, pain, cramping, erythema and induration, most commonly affecting the forearms, wrists and hands, ankles, legs and feet, inability to extend the wrists without flexing the fingers or the elbows, contractures*
Muscle	**Proximal muscle weakness, cramping**
Skeletal	*Arthralgia of large proximal girdle joints and sometimes smaller joints*
Serosal	*Unexplained effusions involving the pleural, pericardial, or peritoneal cavities not due to venocclusive disease of the liver, cardiac insufficiency, malignancy, infection, GM-CSF toxicity or other causes*

C. Laboratory Testing and Diagnostic Indicators of Chronic GVHD

Eye	*Schirmer's test with a mean value ≤ 5 mm at 5 minutes, or values of 6-10 mm in patients who have sicca symptoms, or keratitis detected by slit lamp examination*
Liver	Elevated liver function tests not due to other causes (alkaline phosphatase ≥2 x upper limit, of normal, AST or ALT >3 x upper limit of normal or total serum bilirubin ≥1.6)
Lung	*New obstructive lung defect defined as an FEV1 <80% of predicted with either an FEF 25-75 <65% of predicted or RV >120% of predicted, or a decrease of FEV1/FVC by >12% within a period of less than 1 year, thought not to be caused by an infectious process, asthma or recurrent aspiration from the sinuses or from gastroesophageal reflux. In the absence of GVHD in any other organ, the diagnosis of bronchiolitis obliterans requires negative microbiological tests from bronchoalveolar lavage, evidence of air trapping by high resolution end-expiratory and end-inspiratory CAT scan of the lungs, or confirmation by thoracoscopic biopsy.*
Esophagus	*Esophageal web formation, stricture or dysmotility demonstrated by barium swallow, endoscopy or manometry*
Intestine	Endoscopic findings of mucosal edema and erythema or focal erosions with histological changes of apoptotic epithelial cells and crypt cell drop out. Patients with unresolved acute GVHD may have more severe intestinal mucosal lesions including ulcers and mucosal sloughing.
Muscle	*Elevated CPK or aldolase, EMG findings consistent with myositis with biopsy revealing no other etiological process*
Blood	Thrombocytopenia (usually 20,000-100,000/□l), eosinophilia (> 0.4 x 10^3/uL), hypogammaglobulinemia. Hypergammaglobulinemia and autoantibodies occur in some cases.

D. Guidelines for Treatment of Chronic GVHD after allogeneic HCT

We strongly recommend that you consult the LTFU office before beginning treatment for chronic GVHD and before making changes in immunosuppressive treatment. Clinical trials should always be considered because current standard therapies are associated with high morbidity and decreased survival for patients with high risk chronic GVHD.

Standard treatment of chronic GVHD usually begins with administration of glucocorticoids (1mg/kg/day) followed by taper to eventually reach an alternate-day regimen, with or without daily cyclosporine or tacrolimus (FK506). Other medications used for treatment of corticosteroid-resistant chronic GVHD are summarized on the next page. Telephone consultation with the LTFU medical team is available to you, seven days a week, to discuss appropriate treatment and provide other follow up recommendations. In addition to immunosuppressive treatment, antibiotic prophylaxis for encapsulated bacterial infections and PCP must be given to all patients being treated for chronic GVHD

The duration of systemic immunosuppressive treatment of chronic GVHD varies but requires at least one year of therapy. Approximately 80% of patients require systemic immunosuppressive for 2 years and 40% of them requires therapy for at least 4 years.

Adapted From: Long-Term Followup After Hematopoietic Stem Cell Transplant General Guidelines For Referring Physicians, Fred Hutchinson Cancer Research Center Standard Practice Manual, Section X, Chronic Graft Versus Host Disease (GVHD), Nov/2003 Version

APPENDIX C

ACUTE GVHD ASSESSMENT

Staging by Individual Organ Involvement

SKIN: measured by rash first appearing generally between 10 and 70 days after transplant. (excludes rashes of known viral or other origin)

Stage	Description
1	Maculopapular rash <25% BSA
2	Maculopapular rash 25 – 50% BSA
3	Generalized erythroderma
4	Generalized erythroderma with bullous formation and desquamation

LIVER*: measured by total serum bilirubin

Stage	Description
1	2.0 – 2.9 mg/dL
2	3.0 – 5.9 mg/dL
3	6.0 – 14.9 mg/dL
4	$\geq$ 15.0 mg/dL

GUT:** includes only diarrhea occurring after Day +21

Score	Adult	Pediatric***
1	upper GI (anorexia, nausea, vomiting) with diarrhea of <1000 mL/day	upper GI (anorexia, nausea, vomiting) with diarrhea of <555 mL/m^2/day
2	1000 – 1499 mL/day diarrhea	556-833 mL/m^2/day diarrhea
3	$\geq$ 1500 mL/day diarrhea	>833 mL/m^2/day diarrhea
4	severe abdominal cramping, bleeding or ileus caused by GVHD	

* In cases where another cause of hyperbilirubinemia antedated the onset of rash, the liver score should be decreased by one stage.

** In cases where peak GI symptoms are exacerbated by a cause other than GVHD, the gut score should be decreased by one stage.

*** Pediatric patients <17 years of age

APPENDIX C continued

ACUTE GVHD ASSESSMENT

Overall Grade

The determination of an overall GVHD grade should be based on the organ stage, response to treatment and whether GVHD was a major cause of death.

Overall Grade	Organ Stage	Qualifying Conditions	Additional Qualifying Conditions
I	Stage 1 -2 skin	No liver or gut	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD.
II	Stage 3 skin or Stage 1 liver or Stage 1 gut	N/A	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD, but glucocorticoid treatment after the onset of GVHD was generally sufficient to control the disease.
III	Stage 4 skin or Stage 2-4 liver or Stage 2-4 gut	**without** GVHD as a major contributing cause of death	Indicates that the prophylactic immunosuppressive regimen was not sufficient to prevent all manifestations of aGVHD and that additional treatment after the onset of GVHD did not readily control the disease.
IV	Stage 4 skin or Stage 2-4 liver or Stage 2-4 gut	**with** GVHD as a major contributing cause of death	GVHD was resistant to both the prophylactic immunosuppressive regimen and any additional treatment after the onset of the disease.

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APPENDIX D
GVHD Assessment Form

GVHD assessment form.pdf

APPENDIX E

Evaluation of Disease Response

Chronic myeloid Leukemia (CML)

Complete response:	Normalization of the WBC with complete disappearance of the Ph chromosome in 20/20 metaphases whenever possible. Molecular response is defined by negative RT-PCR for the BCR/ABL transcripts in bone marrow or blood.
Partial response:	Normalization of the white count with >0% but ≤35% Ph-metaphases.
No response:	Persistence of ≥80% Ph-positive metaphases.
Progressive disease:	Acquisition of a new cytogenetic abnormality and/or development of accelerated phase or blast crisis. The criteria for accelerated phase will be defined as unexplained fever greater than 38.3° C, new clonal cytogenetic abnormalities in addition to a single Ph-positive chromosome, marrow blasts and promyelocytes >20%.

Acute leukemia (AML, ALL)

Complete response:	<5% marrow blasts by pathology and no circulating leukemic blasts.
Partial response:	5-30% marrow blasts, or <5% marrow blasts with circulating blasts.
Stable disease:	>30% marrow blasts without definite deterioration of performance status or worsening of anemia, neutropenia, or thrombocytopenia.
Progressive disease:	Evidence of relapse (>5% blasts) by morphologic or flow cytometric evaluation of the bone marrow aspirate or appearance of extramedullary disease.

Chronic lymphocytic leukemia (CLL)

Complete remission:	Normal imaging studies (X-ray, CT, MRI) (nodes, liver, and spleen), peripheral blood by flow cytometry has no clonal lymphocytes, bone marrow by flow cytometry has no clonal lymphocytes, bone marrow by morphology has no nodules (or if present, nodules are free from CLL cells by immunohistochemistry), and the duration is ≥2 months.
CR with minimal residual disease:	Peripheral blood or bone marrow by flow cytometry >0 - <1 CLL cells/1000 leukocytes (0.1%)
Partial remission:	Absolute lymphocyte count in peripheral blood ≥50% decrease[3] and physical exam/Imaging studies (nodes, liver, and/or spleen) ≥50% decrease[3, 4]. Duration is ≥2 months.
Progressive disease:	≥1 of: Physical exam/imaging studies (nodes, liver, and/or spleen) ≥50% increase or new, circulating lymphocytes by morphology and/or flow cytometry ≥50% increase, and lymph node biopsy with Richter's transformation
Stable disease:	Did not meet any of the above criteria for complete or partial remission or progression.
Relapsed disease:	Criteria of progression occurring 6 months after achievement of complete or partial remission.

Lymphoma [Hodgkin's Disease, Non-Hodgkin's Lymphoma (NHL)]

Complete response:	Disappearance of all clinically detectable disease.
Partial response:	≥50% reduction of the sum of the products of the perpendicular diameters of marker lesions, no progression of any existing lesions, and no new lesions.
Stable disease:	Stabilization of all existing lesions with no new lesions (i.e. a <25% increase or <50% decrease in disease parameters defined above throughout the treatment period).

Progressive disease: >25% increase in the sum of the products of the perpendicular diameters of marker lesions, or the appearance of new lesions.

Multiple Myeloma (MM)

Complete response: Disappearance of plasmacytomas; decrease in marrow plasmacytosis to <10%; ≥75% reduction of the monoclonal serum protein. Reduction of the 24 hour urine M-component to ≤10% of the initial prestudy value and to less than 0.2 g/day; no increase in the size or number of lytic skeletal lesions; and normal serum calcium.

Partial response: ≥50%, <75% reduction of the monoclonal serum protein and reduction of the 24 hour urine M-component to <0.2 gm/day; no increase in serum calcium, or in the size or number of plasmacytomas or lytic skeletal lesions.

Stable disease: <50% reduction or <100% increase of the serum myeloma protein.

Progressive Disease: ≥100% increase of the serum myeloma protein from its lowest level, or reappearance of myeloma peaks that had disappeared with treatment; or definite increase in the size or number of plasmacytomas or lytic bone lesions.

Myelodysplasia (MDS)

Progressive Disease: Any evidence by morphologic or flow cytometric evaluation of the bone marrow aspirate of new blasts (>5%).

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[1] Without granulocyte colony stimulating factor support.
[2] Without red blood cell transfusions or erythropoietin support.
[3] Compared to before starting therapy.
[4] Defined by the sum of the products of up to 6 lymph nodes with no increase in the size of any single lymph node (ie, an increase of <25 percent in a lymph node <2cm is not considered significant) and no new enlarged lymph nodes.

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APPENDIX F

Study Coordinator's Manual

I. Introduction

The mixed chimerism protocols have been opened to multiple sites to increase the referral base and accrual. Because of this expansion of collaborators, the data collection procedures are being revised. The procedure manual was created to assure consistency of data reporting across the centers and to assure compliance with regulations. General expectations of collaborators are that they will comply with appropriate regulatory requirements, specified protocol requirements, and provide outcome data.

The manual translates working procedures for study coordination. Its goal is to describe the procedures with sufficient clarity to ensure that all study centers will use the same procedures and follow-up schedules for participant data management and reporting. Changes to the manual and relevant forms will be made as soon as practical and will become effective on receipt of the revised procedures at the study centers, unless otherwise noticed.

II. Institutional Review Board Review of Protocols and Modifications

All research protocols proposed for use that involves human subjects must be reviewed and approved by the Institutional Review Board (IRB) prior to implementation. New protocols will undergo review at the FHCRC IRB and then will be distributed to sites that wish to participate for their IRB's review. For Centers that have a Federal Wide Assurance (FWA), formal collaboration includes submission of a form 310 and a copy of the IRB approved protocol and consent forms to the FHCRC. For sites without a FWA, an FWA form needs to be filed. Once the paperwork is submitted to the Office for Human Research Protection, the approval process can take up to a couple of months, and must be completed before collaboration on a protocol can begin.

In addition, all amendments and/or revisions to on-going, approved activities must be submitted for review and approved prior to implementation at an institution. No revisions may be implemented at outside institutions without the prior approval of the FHCRC Principal Investigator. The FHCRC and the local site's IRB must review all protocol activities at least once annually. This must be done within 365 days of the last review. A copy of annual renewal approvals must be received for collaboration to continue for the next year.

III. Registrations

Collaborating Institutions: The principal investigator of the collaborating institution who will register the patient with the FHCRC will identify eligible patients. Registration will include completion of the eligibility checklist/demographic form. This form will be faxed (206-667-5378) prior to treatment initiation. Patients should be registered prior to treatment initiation for valid registration

IV. Reporting Adverse Events

The following guidelines are the minimum serious adverse event (SAE) reporting guidelines for Category 1 and 2 studies conducted at the Fred Hutchinson Cancer Research Center.

Expedited Reporting Requirements

All adverse events (whether occurring on-site or off-site), which in the opinion of the principal investigator are (1) unexpected, and (2) related or possibly related to the research and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized must be submitted to the IRB within ten (10) calendar days of becoming aware of the event.

Definitions

An Adverse Event - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, medical treatment or procedure and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical treatment or procedure whether or not considered related to the medicinal product.

Related or Possibly Related Adverse Event: An adverse event is "related or possibly related to the research procedure" if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. Adverse events that are **solely** caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not "related or possibly related." If there is any question whether or not an adverse event is related or possibly related, the adverse event should be reported.

Serious Adverse Event: An adverse event that results in any of the following outcomes:

- death
- a life-threatening adverse event (real risk of dying)
- unplanned inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity/or change in psychosocial status
- a congenital anomaly
- requires intervention to prevent permanent impairment of damage

- *Life-threatening AE* is defined as any adverse event that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction.

Unexpected Adverse Event: An adverse event is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the known or foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document and other relevant sources of information such as product labeling and package inserts; and are also not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition or any predisposing risk factor profile for the adverse event.

To ensure no confusion or misunderstanding exist of the differences between the terms "serious" and "severe," which are not synonymous the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) or a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is *not* the same as "serious," which is based on patient/event *outcome or action* criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory obligations.

For example, hospitalization, in general, will not be considered a serious adverse event as approximately half of evaluable MRD patients AND the majority of evaluable URD patients receiving non-myeloablative transplants were hospitalized. Hospitalization will be considered a serious adverse event if it fulfills the criteria for a serious and unexpected adverse event as described above.

Serious events, including deaths, due to GVHD and/or infections will not be reported on an expedited basis. These are well documented, expected, post transplant complications and will be reported biannually to the DSMB.

FHCRC is acting as the Coordinating Center for this multi-institutional study, and it is the responsibility of the FHCRC Principal Investigator (or designee) to complete the FHCRC Serious Adverse Event Report for all serious adverse events that meet the expedited reporting requirements that are received from the participating sites. It is the responsibility of the FHCRC Principal Investigator to notify the sponsor, NIH, FDA or other agencies of serious adverse events as required in the protocol.

Procedure for Reporting Serious and Unexpected Adverse Events (SAE) from Participating Sites: Regulations defining the responsibilities for reporting serious and unexpected adverse reactions are defined above.

Donor: SAEs or any death regardless of cause (serious, unexpected, and related/possibly related) will be monitored and recorded from the time the donor starts atorvastatin therapy through 7 days after the discontinuation of the medication. These must be reported to the FHCRC Investigator within 10 days of learning of the event.

Recipient: SAEs (life-threatening or fatal)

- **For 2546 as an adjunct to treatment plan or primary protocol**, SAEs or any death regardless of cause (serious, unexpected, and related/possibly related) will be monitored and recorded from the time the recipient starts conditioning therapy through day 100 or discharge from the center, whichever occurs earlier. These must be reported to the FHCRC Investigator within 10 days of learning of the event.
- **For 2546 as an adjunct to a nonmyeloablative investigational protocol**, follow reporting guidelines of nonmyeloablative investigational protocol.

The immediate telephone report must be followed by faxed comments to the FHCRC Trial Coordinator at **(206) 667-5378.** This will be followed by detailed written report (See **Appendix G**) within 10 working days. The report must include the date and time of onset, severity and duration of the event, the relationship to the study, the treatment given and eventual outcome. Follow-up information to a SAE report must be submitted as soon as the relevant information is available.

Reporting of Adverse Events on Case Report Forms (CRF)
All grade 3 or 4 adverse events (or highly unusual grade 2 adverse events), which occur between start of conditioning and day 100 during the study will be recorded on the CRF. These adverse events which are observed by the Investigator or reported by the patient, whether or not attributed to the study, will be reported on the Case Report Form using the selected (for this protocol) NCI Common Toxicity Criteria (NCI-CTC) version 4 (**Appendix J**). Attributes will include a description, date of onset, maximum severity, and assessment of relationship to the study agent or other suspect agent(s). These grade 3 or 4 adverse events will be reported to the DSMB as part of the biannual review of the protocol. The DSMB report is submitted with the annual IRB renewal.

For 2546 adjunct to a treatment plan (FHCRC or Outside Center)
Only SAEs (life-threatening or fatal) will be captured on SAE form (Appendix G). No other grade 3 or 4 Adverse Events will be captured.

Reporting of Unanticipated Problems that Involve Risk to Research Participants or Others: Any incident, experience, or outcome that meets both of the following criteria:

- Unexpected (in terms of nature [specificity], severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Indicates that the research places research participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

These must be reported to the FHCRC Investigator within 10 days of learning of the event as described above for reporting of SAE.

V. **Case Report Forms**

Donor CRFs – safety evaluations at three timepoints (CRFs to be provided to external sites) (Appendix M)

- Prior to start of statins
- First day of collection
- 7 days post collection

Recipient CRFs

For 2546 as an adjunct to treatment plan or primary protocol

- Acute GVHD grading form at approximately Day 100 (Appendix D)
- Patient status on an ongoing basis

For 2546 as an adjunct to a nonmyeloblative investigational protocol

- Follow CRF guidelines and instructions of nonmyeloblative investigational protocol.

VI. Protocol Monitoring

The guidelines below are intended to guide the reviewers in their assessment of items that significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity.

A. Registration/Randomization
   1. Patient was registered prior to treatment and approval by FHCRC PI occurs prior to randomization.
   2. Information given at registration represents actual data in medical records (stage, diagnosis, cell type, etc.)

B. Informed Consent/IRB Approval Dates
   1. The consent was signed prior to registration
   2. The consent is in language was approved by the IRB. IRB approval and reapproval are documented including appropriate use of full-board review and proper review of appropriate amendments or revisions
   3. Consent was dated and has written witness signature. IRB approval was obtained prior to the patient signing the consent form and start of treatment.

C. Patient Eligibility
   1. Eligibility criteria and exclusion criteria were met
   2. Treatment/Intervention Administration
   3. Doses were modified according to protocol
   4. Accurate documentation of drug administration

D. Study Tests/Evaluation
   1. Protocol specified laboratory tests or diagnostic studies are available
   2. Appropriate record of protocol intervention is documented.

E. Study Events/Adverse Drug Experience
   1. Serious Adverse Evens reported according to protocol specifications

F. Follow-Up
   1. Disease status assessed according to the required protocol guidelines documenting response to treatment.
   2. Accurate determination of cancer progression

APPENDIX G
Serious Adverse Event Report
Protocol 2546

1. Patient's Name:

2. Date of Serious Adverse Event:

3. Nature of Serious Adverse Event:

4. Reasons for AE classification as serious: *(mark all that apply)*

- ☐ Death
- ☐ New hospitalization
- ☐ Prolongation of current hospitalization
- ☐ Urgent medical intervention to prevent death or disability
- ☐ New persistent or exacerbation of significant disability or incapacity

5. Specify any agent(s) suspected of causing adverse event:

#1

6. Describe the Serious Adverse Event *(or attach a copy of relevant medical records or FDA MedWatch Form)*.

7. Signature of Reporter _____/___/_____
Date

8. PI assessment

Adverse event possibly, probably or definitely related to investigational agent(s)? ○No ○Yes
Adverse event ○expected ○unexpected (not listed in protocol, consent, product label or drug brochure)
Expedited report to FHCRC IRB is needed if serious adverse event is unexpected and related to investigational agent.

9. Signature of P.I. _____/___/_____
Date

APPENDIX H

Notice of Death

Patient ID: _____ Date of Death: _____

Place of Event: _____

Apparent cause of death (Please be specific. Attach hospital summary or death summary when possible):

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Form completed by: _____Date: _____

APPENDIX I

COORDINATING CENTER FUNCTIONS

Outside Center – PI Communication in Hematologic Malignancies

I. Study Management, data analysis, and Data and Safety Monitoring

a. Study Management:
   i. Each local PI is responsible for selection, training and oversight of local study coordinators
   ii. The Coordinating Center registers subjects on the study and assigns study IDs
   iii. One copy of the research data is retained by the site. Another data set (identified only by study IDs) is transmitted to the Coordinating Center to create the master data file. All data are kept in locked areas and password protected databases accessible only to study staff
   iv. The quality of data is monitored in an ongoing fashion with the study team and corrective action plans instituted as necessary

b. Data Analysis:
   i. Study staff review data for completeness as it is submitted by the sites
   ii. The study statistician is responsible for data cleaning and the conduct of analyses as outlined in the protocol and grant

c. Data Safety and Monitoring:
   i. The trial coordinators at collaborating centers or the local PIs will fax an official report of an SAE (as defined by the protocol) to the Coordinating Center within ten days.
   ii. The SAE report is reviewed by the Overall PI. If the SAE meets the FHCRC criteria for reporting then an official signed report is submitted to the IRB
   iii. An independent DSMB will meet at six-month intervals and all outcome data is reviewed including all adverse events and SAEs reported to the Coordinating Center along with those officially reported to the IRB
   iv. A report from the DSMB is submitted to the IRB as well as the trial coordinators/local PIs participating in the protocol

II. Protocol and informed consent document management

a. A master protocol is maintained by the Coordinating Center and distributed to the sites for customization and local IRB review
b. All protocol and consent modifications initiated by the Coordinating Center are sent to the Collaborating Sites following approval by the Coordinating Center IRB, for review and approval by the local IRB
c. Changes required by local IRBs are reviewed by the Coordinating Center and approved prior to implementation at local sites

III. Assurance of local IRB OHRP-approved assurance

a. Each site provides their OHRP assurance number and evidence of IRB certification
b. Study staff monitor maintenance of institutional assurance and IRB certification

IV. Assurance of local IRB approvals

a. The Coordinating Center maintains copies of the most current collaborating site Consent Forms and IRB approval documentation
b. No site may enroll subjects until the Coordinating Center has received confirmation of local IRB approval
c. Each site is responsible for preparation and submission of their continuing reviews. Any changes to the protocol or consent form will be communicated to the Coordinating Center

d. Sites are required to have active IRB approvals to participate in any study related activities

V. Any substantive modification by the Collaborating Institution related to risks or alternative procedures is appropriately justified

a. The Coordinating Center reviews any modifications to consent forms to ensure that site consents do not delete or change the basic or additional elements or alternatives required in the sample consent form

VI. Informed consent is obtained from each subject in compliance with HHS regulations

a. Subjects must provide written informed consent prior to study participation
b. The Coordinating Center verifies eligibility and signed consent prior to assigning a study ID number

APPENDIX J

Adapted from
COMMON TOXICITY CRITERIA (CTC)
Version 4.0

Grade			
Adverse Event	**3**	**4**	**5**
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Disseminated intravascular coagulation	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Febrile neutropenia	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Hemolysis	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Hemolytic uremic syndrome	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Grade			
Adverse Event	**3**	**4**	**5**
CARDIAC DISORDERS			
Atrial fibrillation	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Atrial flutter	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Atrioventricular block complete	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Constrictive pericarditis	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death

Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Left ventricular systolic dysfunction	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Myocardial infarction	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Myocarditis	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Pericardial effusion	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Pericardial tamponade	-	Life-threatening consequences; urgent intervention indicated	Death
Ventricular arrhythmia	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
GASTROINTESTICAL DISORDERS			
Ascites	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Diarrhea	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Duodenal ulcer	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Gastric ulcer	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Gastritis	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Lower gastrointestinal hemorrhage	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Mucositis oral	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Oral hemorrhage	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pancreatitis	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Typhlitis	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
GENERAL DISORDERS AND ADMINISTARTION SITE CONDITIONS			
Multi-organ failure	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Grade			
Adverse Event	**3**	**4**	**5**
HEPATOBILIARY DISORDERS			

Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
IMMUNE SYSTEM DISORDERS			
Allergic reaction	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Immune system disorders - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
INFECTIONS AND INFESTATIONS			
Enterocolitis infectious	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Infections and infestations - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**

INVESTIGATIONS			
Alanine aminotransferase increased	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Aspartate aminotransferase increased	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Blood bilirubin increased	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Carbon monoxide diffusing capacity decreased	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g. , >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Cardiac troponin I increased	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Cardiac troponin T increased	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Creatinine increased	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Weight gain	>=20% from baseline	-	-
Grade			
Adverse Event	**3**	**4**	**5**
METABOLISM AND NUTRITIONAL DISORDERS			
Hypercalcemia	Corrected serum calcium of >12.5 - 13.5 mg/dL;>3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Hypertriglyceridemia	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Tumor lysis syndrome	Present	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INC CYSTS AND POLYPS)			
Treatment related secondary malignancy	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Grade			

Adverse Event	3	4	5
NERVOUS SYSTEM DISORDERS			
Dysarthria	Severe impairment of articulation or slurred speech	-	-
Intracranial hemorrhage	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Ischemia cerebrovascular	-	-	-
Leukoencephalopathy	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Syncope	Fainting; orthostatic collapse	-	-
Nervous system disorders - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
RENAL AND URINARY DISORDERS			
Chronic kidney disease	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Renal and urinary disorders - Other, specify	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**

REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Grade			
Adverse Event	**3**	**4**	**5**
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS			
Adult respiratory distress syndrome	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Apnea	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Bronchopulmonary hemorrhage	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Hypoxia	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Pleural effusion	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Pneumonitis	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Pulmonary edema	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Respiratory failure	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Grade			
Adverse Event	**3**	**4**	**5**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			

Erythema multiforme	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
		Grade	
Adverse Event	**3**	**4**	**5**
VASCULAR DISORDERS			
Capillary leak syndrome	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypotension	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Thromboembolic event	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Vasculitis	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death

APPENDIX K
Protocol 2546 Patient Demographics and Eligibility Form

UPN#:_____

Patient Name: _____ _____ _____
(Last) *(First)* *(MI)*

Date of Birth: _____ / _____ / _____ *(Mo) (Day) (Year)* **Age**:_____

Gender *(choose one):*
☐ Male ☐ Female ☐ Unknown

Patient Diagnosis: _____

Planned Day 0: _____/_____/_____
(Mo) (Day) (Year)

Ethnicity *(choose one): Instruct the patient to select one of the following.*

- ☐ **Hispanic** *(A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. Term "Spanish Origin" can also be used in addition to "Hispanic" or "Latino".)*
- ☐ **Not Hispanic or Latino**
- ☐ **Declined to Report**

Race *(check all that apply): Instruct the patient to select one or more of the following.*

- ☐ **American Indian/Alaska Native** *(A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment).*
- ☐ **Asian** *(A person having origins in any of the original peoples of the Far East, Southeast, Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam).*
- ☐ **Black/African American (***A person having origins in any of the black racial groups of Africa).*
- ☐ **Native Hawaiian/Pacific Islander** *(A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands).*
- ☐ **White** *(A person having origins in any of the original peoples of Europe, the Middle East or North Africa).*
- ☐ **Research subject does not know race**
- ☐ **Declined to report**

The PI confirmed that patient should receive Fludarabine and TBI (If no autologous transplant within 6 months or equivalent high-dose therapy without HCT).

☐Yes ☐ No Date: _____ PI Initials: _____

CRITERIA FOR 3 GY TBI (only for patients in Regimen A, Flu/TBI): Patients need to fulfill one or more of the following criteria for 3 Gy TBI:

☐ Patients with MDS, MPD, CML, or other hematologic malignancies not previously treated with myelosuppressive chemotherapy
☐ Patients who have had a previous allogeneic transplant.
☐ Patients who had a prior syngeneic transplant without subsequent myelosuppressive chemotherapy.
☐ Patients who have not had myelosuppressive chemotherapy within 3-6 months of HCT may be at higher risk of rejection depending on treatment history and underlying diagnosis. Confirm TBI dose (2 vs 3 Gy) with PI.

CRITERIA FOR 4 Gy TBI:

☐ For outside centers only, 4 Gy TBI may be used when the protocol serves as adjunct to a reduced intensity treatment plan that includes 4 Gy TBI.

TBI Dose:

☐ TBI 2 Gy
OR
☐ TBI 3 Gy:
OR
☐ TBI 4 Gy:

Signature of **Local** Principal Investigator**:** _____ Date: _____

Transplant Center: _____

Signature of **FHCRC** Principal Investigator: _____ Date: _____

Study UPN#: _____

APPENDIX K cont'd

Protocol 2546 Eligibility

☐ 2546 is being used as an adjunct Protocol. Patient is enrolled on an investigational nonmyeloablative HCT protocol or a nonmyeloablative treatment plan with postgrafting CSP that does not use acute GVHD as its primary endpoint.
- Must meet following inclusion criteria 1 ONLY
- Must meet following exclusion criteria 16-18 ONLY

OR

☐ Protocol 2546 serves as an independent primary treatment protocol
- Must meet all following inclusion and exclusion criteria

Inclusion Criteria:

1) Yes ☐ No ☐ HLA-identical sibling donor:

Patient					
A: _____	A:_____	C: _____	C: _____	B: _____	B: _____
DRB1: _____	DRB1:_____	DQB1:_____	DQB1:_____		
Donor					
A: _____	A:_____	C: _____	C: _____	B: _____	B: _____
DRB1: _____	DRB1:_____	DQB1:_____	DQB1:_____		

2) Yes ☐ No ☐ N/A ☐ All children < 12 years must be discussed with the FHCRC PI (Marco Mielcarek, MD 206-667-2827) and by a relevant patient review committee, such as the FHCRC Patient Care Conference (PCC) prior to registration.

3) Yes ☐ No ☐ Patients must have either relapsed after previous high-dose chemotherapy and autologous or allogeneic HCT, or else be ineligible for such an approach due to age, failure to mobilize sufficient hematopoietic stem cells, medical comorbidities, or patient refusal

4) Yes ☐ No ☐ Patients who refuse to be treated on a conventional autologous or allogeneic HCT protocol.

I) One of the following criteria questions (5-15) must be marked "Yes" for the patient to enter on 2546. (The following diseases will be permitted although other diagnoses can be

considered if approved by PCC or the participating institution's patient review committees and the principal investigator.)

5) Yes ☐ No ☐ **Aggressive non-Hodgkin lymphomas (NHL) and other histologies such as diffuse large B-cell NHL** – not eligible for autologous HCT, not eligible for high-dose allogeneic HCT, or after failed autologous HCT.

6) Yes ☐ No ☐ **Mantle Cell NHL** - Diagnostic LP required pre-transplant

7) Yes ☐ No ☐ **Low grade NHL**– with < 6 month duration of CR between courses of conventional therapy.

8 Yes ☐ No ☐ **CLL** – must have either 1) failed to meet NCI Working Group criteria or partial response after therapy with a regimen containing FLU (or another nucleoside analog,) or experience disease relapse within 12 months after completing therapy with a regimen containing FLU (or another nucleoside analog); 2) failed FLU-CY-Rituximab (FCR) combination chemotherapy at any time point; or 3) have "17p deletion" cytogenetic abnormality. Patients should have received induction chemotherapy but could be transplanted in 1st CR; or 4) Patients with a diagnosis of CLL (or small lymphocytic lymphoma) that progresses to prolymphocytic leukemia (PLL), or patients with T-cell CLL or PLL

Describe which inclusion is specific for this patient:_____

9) Yes ☐ No ☐ **Hodgkin lymphoma** – must have received and failed frontline therapy.

10) Yes ☐ No ☐ **Multiple Myeloma** – must have received prior chemotherapy. Consolidation of chemotherapy by autografting prior to nonmyeloablative HCT is permitted.

11) Yes ☐ No ☐ **Acute Myeloid Leukemia (AML)** – must have < 5% marrow blasts at the time of transplant.

12) Yes ☐ No ☐ **Acute Lymphocytic Leukemia (ALL)** – must have <5% marrow blasts at the time of transplant.

13) Yes ☐ No ☐ **Chronic Myeloid Leukemia (CML)** – Patients will be accepted if they have shown intolerance to tyrosine kinase inhibitors or are beyond CP1 and if they have received previous myelosuppressive chemotherapy or HCT, and have <5% marrow blasts at time of transplant.

14) Yes ☐ No ☐ **Myelodysplasia (MDS)/Myeloproliferative Syndrome (MPS)** –must have <5% marrow blasts at time of transplant.

15) Yes ☐ No ☐ **Waldenstrom's Macroglobulinemia –** must have failed 2 courses of therapy.

II) Exclusion criteria:

Each of the following questions must be marked "No" Or "NA" for the patient to enroll on 2546.

16) Yes ☐ No ☐ Patient will undergo a myeloablative preparative regimen.

17) Yes ☐ No ☐ Patient is participating in an investigational study that has acute GVHD as the primary endpoint

18) Yes ☐ No ☐ The allogeneic PBSC donor has a contraindication to statin treatment.

19) Yes ☐ No ☐ Patients eligible for and willing to receive potentially curative high dose chemotherapy and autologous HCT

20) Yes ☐ No ☐ **Organ dysfunction.** Please check yes if patient meets any of the following.

Yes ☐ No ☐ **Cardiac:** ejection fraction < 30% on MUGA scan or cardio echo or active symptomatic coronary artery disease. Patients with cardiac disease should be evaluated with appropriate cardiac studies and/or cardiology consultation as clinically indicated.

Yes ☐ No ☐ **Pulmonary:** DLCO < 40%, TLC <30%, FEV1 <30% and/or receiving supplementary continuous oxygen.

Yes ☐ No ☐ **Liver function abnormalities**: Patients with clinical or laboratory evidence of liver disease should be evaluated in conjunction with the GI consult service for the cause of liver disease, its clinical severity, and the degree of portal hypertension. Patients will be excluded if they are found to have fulminant liver failure, cirrhosis of the liver with evidence of portal hypertension, bridging fibrosis, alcoholic hepatitis, esophageal varices, a history of bleeding esophageal varices, hepatic encephalopathy, refractory ascites related to portal hypertension, bacterial or fungal liver abscess, chronic viral hepatitis with total serum bilirubin >3 mg/dL, or actively symptomatic biliary disease.

Yes ☐ No ☐ Renal: Patients with renal failure are eligible. However, patients with pre-existing renal insufficiency will likely have further compromise in renal function and may require dialysis.

21) Yes ☐ No ☐ Patients who are seropositive for human immunodeficiency virus (HIV).

22) Yes ☐ No ☐ N/A ☐ Women who are pregnant or breast-feeding.

23) Yes ☐ No ☐ N/A ☐ Fertile men or women unwilling to use contraception during HCT and for 12 months afterward

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24) Yes ☐ No ☐ Patients with active non-hematological malignancies (except non-melanoma skin cancers) or those with non-hematological malignancies (except non-melanoma skin cancers) who have been rendered with no evidence of disease, but have a greater than 20% chance of having disease recurrence within 5 years. This exclusion does not apply to patients with non-hematologic malignancies that do not require therapy.

25) Yes ☐ No ☐ Karnofsky score <60 for adult patients or Lansky-Play Performance Score <50 for pediatric patients.

26) Yes ☐ No ☐ Patients with fungal pneumonia with radiological progression after receipt of amphotericin formulation or mold-active azoles for greater than 1 month

Note – the HCT-Comorbidity score is: _____

☐ FHCRC Patients:

Signature of person completing form: _____ Date: _____

Signature of Principal Investigator (signing of consent): _____ Date: _____

Patient signed IRB approved consent form. Date: _____

IRB file number: _____ Date of IRB approval: _____

OR

☐ Outside Center Patients:

Signature of person completing form: _____ Date: _____

Patient signed IRB approved consent form. Date: _____

IRB file number: _____ Date of IRB approval: _____

Signature of **Local** Principal Investigator _____ Date: _____

Signature of **FHCRC** Principal Investigator _____ Date: _____

APPENDIX L
2546 Case Report Form

2546 CRF v.1.0.pdf

APPENDIX M

Protocol 2546 Donor Safety and Compliance Evaluation

Date: _____ Donor: _____
Contact: ☐ phone ☐ in-person Patient: _____

Time point:
___ 1 week post start of atorvastatin
___ PBSC collection
___ 1 week post collection/discharge

Start date of atorvastatin: _____ Last dose (date): _____

Total number of doses taken: _____

Safety

Since the start of atrovastatin therapy have you experienced any of the following symptoms:

Y	N	
☐	☐	muscle pain or tenderness Location: _____
☐	☐	muscle weakness Location: _____
☐	☐	joint pain Location: _____
☐	☐	diarrhea
☐	☐	gas or heartburn
☐	☐	nausea
☐	☐	other Describe: _____

Action/comments:

Labs Comments:

Labs	Pre	Post
Date		
CK		
T Bili		
D Bili		
ALT		
AST		
Alk Phos		
Albumin		

Compliance

Since the last contact, have you missed any doses of atorvastatin? Yes No
If yes, how many doses have been missed? _____

Comments:

Signature Date

APPENDIX N

(Not required when 2546 is being used as an adjunct Protocol)

The Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI) 9/7/10

Assign scores appropriately if the patient has any of these comorbidities

Patient _____(name), UPN_____ Date_____

Comorbidities	Definitions	HCT-CI scores	Actual Lab Values/Comments
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, and ventricular arrhythmias requiring treatment *in the patient's past history*	1	
Cardiac	Coronary artery disease†, congestive heart failure, myocardial infarction *in patient's past history* or EF of ≤50% *at time of HCT*	1	
Inflammatory bowel disease	Crohn's disease or ulcerative colitis requiring treatment *in the patient's past history*	1	
Diabetes	Requiring treatment with insulin or oral hypoglycemic, but not diet alone, *at time of HCT*	1	
Cerebro-vascular disease	Transient ischemic attack or cerebro-vascular accident *in patient's past history*	1	
Psychiatric disturbance	Depression/anxiety requiring psychiatric consult or treatment *at time of HCT*	1	
Hepatic – mild	Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN *at time of HCT*	1	
Obesity	Patients with a BMI of >35 for adults or with BMI-for-age percentile of ≥ 95th percentile for children *at time of HCT*	1	
Infection	Documented infection or fever of unknown etiology requiring anti-microbial treatment *before, during and after* the start of conditioning regimen	1	
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica *in patient's past history*	2	
Peptic ulcer	Requiring treatment *in patient's past history*	2	
Renal	Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation *at time of HCT*	2	
Moderate pulmonary	DLco and/or FEV_1 >65%-80% or Dyspnea on slight activity *at time of HCT*	2	
Prior solid tumor	• *Treated at any time point* in the patient's past history*, excluding non-melanoma skin cancer*	3	
Heart valve disease	*At time of HCT* excluding mitral valve prolapse	3	
Severe pulmonary	DLco and/or FEV_1 ≤65% or Dyspnea at rest or requiring oxygen *at time of HCT*	3	
Moderate/severe hepatic	Liver cirrhosis, Bilirubin >1.5 X ULN, or AST/ALT >2.5XULN *at time of HCT*	3	
Please provide (KPS):	**Karnofsky Performance Score = _____%**	***Total Score =_____***	**Signature of Provider: _____**

†One or more vessel-coronary artery stenosis, requiring medical treatment, stent, or bypass graft.

EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide; FEV_1, forced expiratory volume in one second; AST, aspartate aminotransferase; ALT, alanine aminotransferase.