FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE,
DEPARTMENT OF MEDICINE, DIVISION OF ONCOLOGY
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1. Title of protocol: Sequential Autologous HCT / Nonmyeloablative Allogeneic HCT using Related, HLA-Haploidentical Donors for Patients with High-Risk lymphoma, Multiple Myeloma, or chronic lymphocytic leukemia

Investigators:

Mohamed L. Sorror, MD/MSc	Associate Member, Clinical Research, FHCRC; Associate Professor of Medicine, UW (206-667-6298);
David G. Maloney, MD/PhD	Member, FHCRC, Associate Professor of Medicine, UW (206-667-5616);
Brenda M. Sandmaier, MD	Member, FHCRC, Professor of Medicine, UW (206-667-4961);
Paul Martin, M.D	Member, FHCRC; Professor of Medicine, UW;
Effie Petersdorf, M.D	Member, FHCRC; Associate Professor of Medicine, UW;
Ann Woolfrey, MD	Member, FHCRC; Professor of Pediatrics, UW;
William Bensinger, MD	Member, FHCRC, Professor, UW (206-667-4933);
Leona Holmberg, MD, PhD	Member, FHCRC, Associate Professor of Medicine, UW (206-667-6447);
Rainer Storb, MD	Member, FHCRC, Professor of Medicine UW (206-667-4407).

Biostatistician: Barry Storer, Ph.D., Member, FHCRC, (206)-667-6151.
Radiation Oncologist: Ralph Ermoian, MD (206)-598-4100
Research staff:
Research Nurse: Michelle Bouvier, RN (206) 667-6993, pager (206) 995-7658

2. Introduction

Patients with advanced lymphoma, multiple myeloma (MM), or chronic lymphocytic leukemia (CLL) have poor curative treatment options. High dose therapy followed by autologous hematopoietic cell transplantation (HCT) has been shown to be of benefit for patients with chemotherapy-sensitive relapsed lymphoma and multiple myeloma (MM) with 3-year disease-free survival (DFS) in the range of 30-65%.**[1-7]** Among lymphoma patients with chemotherapy-resistant or untested relapse, DFS ranged between 0-13%.**[1,8-12]** Similarly, patients with MM, though had survival prolongation compared with chemotherapy, eventually relapsed and died. **[13]** Limited data are available on the long- term efficacy of autologous HCT for CLL patients. **[14-16]**

Allogeneic HCT after myeloablative conditioning resulted in prolonged remissions and low relapse rates for advanced lymphoma, MM, and CLL; but on the expense of relatively high (up to 60%) non-relapse mortality (NRM) even among patients younger than 50 years and with good performance status (PS). **[16-20]** Our nonmyeloablative conditioning regimen of 2 Gy total body irradiation (TBI) alone or with 90 mg/kg of fludarabine before allogeneic HCT have resulted in lessened NRM among a cohort of patients at least 10 years older than those historically offered myeloablative HCT with evidence of control of many hematological malignances. **[21-28]**

Clinical studies at our institution have shown that nonmyeloablative allografts from HLA-related or unrelated donors for MM were most effective when performed in patients with low tumor burden. Cytoreductive autografts performed 40-120 days before nonmyeloablative allografts significantly improved CR rates without increasing the low NRM rates seen with nonmyeloablative allografts alone. **[21,28]** A more recent prospective study using Mendelian randomization suggested superior overall survival among patients with newly diagnosed MM after treatment with one autologous HCT followed by nonmyeloablative allografts from HLA-identical sibling donors compared to those given tandem autografts. This approach allowed temporal separation between the high dose conditioning and the GVT effects with NRM of 18% **[29]**. The same approach has been used for patients with advanced aggressive B cell malignancies with NRM and OS of 16% and 55% at 3-years, respectively (protocol 1409 and unpublished results).

Nevertheless, the chance of the patient's sibling to be HLA genotypically identical is only 25%. The chances of finding suitably phenotypically matched unrelated donors range from 60-70% for Caucasians to <10% for ethnic minorities. **[30,31] [32]** Recently, investigators at John Hopkins Medical School (Protocol #J9966) and FHCRC (Protocol #1667.00) have used nonmyeloablative conditioning with 2 Gy TBI and fludarabine, 150 mg/m^2, in addition to cyclophosphamide administered before and after HLA-haploidentical related HCT to facilitate engraftment and delete alloreactive donor T-cell clones presumably involved in GVHD. Sixty-eight patients with advanced hematological malignancies have been studied. While NRM was relatively low at 1-year (19%), the rate of relapse was 50% at 1-year resulting in overall survival (OS) and DFS rates of 45% and 32%, respectively. **[33]**

Here, we propose to explore the tandem approach of cytoreductive autologous HCT followed by nonmyeloablative HCT from HLA-haploidentical related donors for patients with relapsed/refractory MM, lymphoma, or CLL. We hypothesize that the high dose chemotherapy and/or myeloablative TBI preceding the autologous HCT will provide powerful cytoreduction and achieve a state of minimal disease. This will be augmented 40-120 days later by GVT effects associated with HLA-haploidentical related HCT. We hope to achieve lower relapse rates than noted with the single HCT approach while preserving the low NRM associated with nonmyeloablative conditioning resulting in improved DFS in patients with advanced lymphoma, MM, or CLL.

3. Background

A. Conditioning regimens for autologous HCT

1. Lymphoma or CLL patients

Several different conditioning regimens involving chemotherapy +/- TBI have been used before autologous HCT of patients with lymphoma or CLL. [34-36] Cy/TBI or BEAM given as proposed in this protocol should provide cytoreduction for refractory or relapsed lymphoma or CLL while being well tolerated, with rapid recovery allowing patients to the HLA-haploidentical allograft.

The Cy/TBI conditioning regimen for autologous HCT has proven effective and resulted in high response rates (60-80%) and low NRM (in the range of 1-9%) in patients with refractory and relapsed lymphoma. Three-year DFS has ranged from 27 to55% suggesting that relapse remains the greatest cause of treatment failure. [5,37,38] Similar to results after Cy/TBI, 100 day NRM after BEAM ranged between 2.7 to10%, while 3-year DFS ranged from 40 to 62%.[10-12,39-42] The majority of clinical trials with autologous HCT for patients with CLL have investigated CY/TBI conditioning [16,43-46] and one trial investigated Cy/TBI and BEAM[47] with similar incidences of NRM to that seen in patients with lymphoma (range 0-9%).

To date, however, no comparative randomized trials have been performed comparing regimens In general, a transplant center's choice of regimen is based on experience with the regimens through local or national clinical trials. [36] We have elected, based on our experience, to use either cyclophosphamide and TBI (Cy/TBI), or BEAM for conditioning before autologous HCT. Use of either regimen for each enrolled patient will be decided by the Principal Investigator (PI) with preference for BEAM in patients who have previously received dose-limiting radiation or have high comorbidity scores.

No randomized trials have compared conditioning with chemotherapy alone to chemotherapy + TBI for autologous HCT for relapsed lymphoma or CLL and the optimal approach remains undetermined. In general, a transplant center's choice of regimen is based on experience with the regimens through local or national clinical trials. [36] Retrospective reviews showed no differences in outcomes. [48-51] However, subset analyses have identified two main limitations for the use of TBI-based conditioning regimens, one is the hazard of delivering TBI to patients who have received dose limiting radiation to vital organs. [52] The second limitation is the burden of pretransplant comorbidities, as summarized by the HCT-specific comorbidity index (HCT-CI) [53], where patients with scores of ≥3 experienced 2-year NRM of 25% versus 5% after TBI-based versus BEAM regimens, respectively. [54]
We have elected, based on our experience, to use either cyclophosphamide and TBI (Cy/TBI), or BEAM for conditioning before autologous HCT. Use of either regimen for each enrolled patient will be decided by attending physician after discussion with the Principal Investigator (PI) with preference for BEAM in patients who have previously received dose-limiting radiation [52] *or have high comorbidity scores.* [54]

2. MM patients

High-dose therapy with autologous hematopoietic cell transplantation (HCT) for advanced-stage myeloma in patients less than 65 years of age has survival advantages compared with conventional therapy. [6,55] In the Intergroupe Francais du Myélome (IFM) 90 trial, not only the CR rate, but the 7-year DFS of 16% and OS of 43% were higher than those (8% and 25%) with conventional chemotherapy, respectively. [6,7] With high response rates and relatively low NRM of less than 10%, fewer than 30% of patients remain in remission 3 to 7 years later. [56-62] While a number of conditioning regimens have been used, melphalan at 200 mg/m^2 has been well tolerated, even in patients

in their seventh decade of life, [63-65] and has generally been accepted as the current standard. [64] Conditioning with melphalan at 140 mg/m^2 will be reserved for patients older than 70 years, or those with significant renal insufficiency, or high comorbidity scores.

B. Tandem autograft/ nonmyeloablative allograft with HLA-matched donors

Initially, nonmyeloablative allografts from HLA-matched related donors were used to treat 13 patients with relapsed/refractory MM. This resulted in relatively low NRM (2 patients), while 54% developed progressive disease. In a subsequent MM-specific protocol (#1383), the combination of a cytoreductive autograft using 200 mg/m^2 melphalan with nonmyeloablative allograft was explored. Fifty four patients were enrolled in this tandem approach. [21] Median age was 52 (range 29-71) years, and 48% of patients had relapsed or refractory disease at time of HCT. Patients experienced medians of 0 days of hospitalization, neutropenia, and thrombocytopenia. With a median follow up of 552 days, OS was 78%. Overall response rate was 83% and 57% were in CR. A recent update included 102 patients treated with the same approach with median follow up of 5 years. [29] Thirty-four percent of patients had chemo-refractory disease at time of HCT. Grades II-IV and III-IV acute GVHD were seen in 41% and 8% of patients respectively, while 69% had extensive chronic GVHD. Cumulative incidences of NRM at 100 days, 1-year, and 5-year were 1%, 13%, and 19%, respectively. Overall response rate was 94% (63% were in CR). The 5-year rates of OS and PFS were 63% and 35%, respectively. These results suggested that the low NRM after either transplant modality could be preserved by the tandem approach. Longer follow up is required to determine the durability of the observed high response rates.

Investigators from Italy have shown that planned tandem autografts/ nonmyeloablative allografts from HLA-matched related donors were associated with superior outcomes compared to tandem autografts. [66] In this trial 162 consecutive patients with newly diagnosed myeloma were enrolled. All patients were initially treated with vincristine, doxorubicin, and dexamethasone (VAD), followed by high dose melphalan and autologous stem-cell rescue. Patients with HLA-identical siblings then received nonmyeloablative HCT, while those without HLA-identical siblings received a second autologous HCT. With a median follow-up of 45 months, the median OS and DFS were longer in the 80 patients with HLA-identical siblings than in the 82 patients without HLA-identical siblings (80 months vs. 54 months, P=0.01; and 35 months vs. 29 months, P=0.02, respectively). Among patients who completed their assigned treatment protocols, NRM was comparable among recipients of the double-autologous-transplant group (46 patients) and the autograft-allograft group (58 patients, P=0.09), but disease-related mortality was significantly higher in the double-autologous-transplant group (43% vs. 7%, P<0.001). The authors concluded that among patients with newly diagnosed myeloma, survival in recipients of a tandem autologous/allogeneic HCT from HLA-identical siblings was superior to that of recipients of tandem autografts.

The tandem autologous/ nonmyeloablative allogeneic HCT from HLA-matched unrelated donors was explored in 13 patients with poor-risk MM and the results were compared to those given only nonmyeloablative allogeneic HCT. Patients given the tandem autologous-unrelated HCT versus the single unrelated HCT had higher overall response rate (77% compared to 18%, respectively, p=0.01). PFS was 51% compared to 11%, respectively (p=0.03).

The tandem autologous-related HCT approach is also being investigated in the setting of lymphoma/CLL. To date, 33 patients have received autologous HCT followed after a median of 65 days with nonmyeloablative allogeneic HCT from HLA-matched related (n=25) or unrelated donors (n=8). Diagnoses were NHL (n=22), HL (n=7), or CLL (n=4). Median patient age was 49 years and number of prior regimens was 4 (range 1-12). Thirty-six percent of patients had disease responsive to the last chemotherapy before autografting [6% were in complete remission (CR)] while 46% and 18% had refractory and progressive

disease, respectively. Most patients had aggressive disease (82%). Conditioning for autografts consisted of BEAM (48%) or Cy/12 Gy TBI (52%). At allografting, 52% of patients had CR/PR (15%/37%), 12% stable disease, 3% relapse, and 33% refractory disease. After allogeneic HCT, 24 patients became neutropenic for a median of 13 days and 23 patients had thrombocytopenia (<20,000 cells/ul) for a median of 5 days. All 33 patients had sustained engraftment. Incidences of grades II, III, and IV acute GVHD were 44%, 19%, and 0% respectively, and chronic GVHD was 51%. With median follow up of 39 (range 10-87) months, the overall response rate was 63% (51% CR). Estimated 2-year rates of non-relapse mortality, relapse, overall, and progression-free survivals from the time of autografting were 16%, 38%, 55%, and 47% respectively.

C. John Hopkins and FHCRC experience of nonmyeloablative conditioning and HLA-haploidentical HCT

Pre-clinical data from a mouse model of H-2 haploidentical HCT have shown that the addition of cyclophosphamide before HCT was synergistic with fludarabine in preventing graft rejection and increasing the percent of donor chimerism. ***[67, 68]*** In addition, post transplantation Cy attenuated lethal and non-lethal GVH reactions. ***[67]*** Based on these data, two subsequent clinical trials were initiated for treatment of patients with high-risk hematological malignancies with nonmyeloablative HCT from related, HLA-haploidentical donors (Protocol J9966, Johns Hopkins and 1667 at FHCRC). Conditioning regimen was modified from the regimen developed by Storb and colleagues ***[69]*** and is detailed in Figure 1. Preliminary results demonstrated that partially HLA-mismatched bone marrow can engraft rapidly and stably after nonmyeloablative conditioning that included post-transplantation Cy. ***[70]***

A recent update of the results of these two trials incorporated 68 consecutive patients diagnosed with poor risk hematological malignancies except for one patient with paroxysmal nocturnal hemoglobinuria. {Luznik, O'Donnell, et al. 2008 34429 /id} Patients were treated on two protocols (Protocol J9966, Johns Hopkins and 1667 at FHCRC), which differed by postgrafting immunosuppression. Twenty-one patients (31%) had failed at least one autologous HCT: 12 of 13 patients with HL, 4 of 10 patients with NHL, 3 of 27 patients with acute myeloid leukemia (AML), and one patient each with CLL and MM. Twenty-five percent of patients were from ethnic minority groups. Half (33 of 68) of the donors were siblings of patients, and about a quarter each were either parents or children (19 of 68 and 16 of 68, respectively). Donors and recipients were mismatched by a median of 4 HLA loci in both the host-versus-graft (HVG) and GVH directions.

Median times to neutrophil and platelet recoveries were 15 and 24 days, respectively. Graft rejections occurred in 9 of 66 evaluable patients (13%). All but 1 patient with graft failure experienced recovery of autologous hematopoiesis. Among engrafting patients, achievement of full donor chimerism was rapid and >95% by 2 months after transplantation.

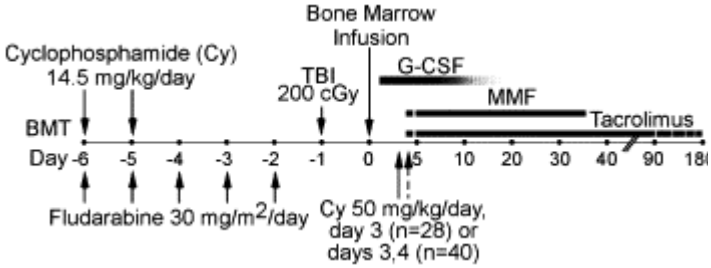

Figure 1. Nonmyeloablative haploidentical BMT conditioning and postgrafting immunosuppressive regimen.

The median number of hospitalizations prior to day 60 was 1 (range: 0-4), and the median length of stay was 4 days (range: 0-66). Neutropenic fever accounted for 51% of the admissions, nonneutropenic infections accounted for 22%, aGVHD accounted for 9%, and other causes were the reason for the remaining 19% of admissions. A total of 22 patients (32%) did not require hospitalization within the first 60 days of transplantation.

CMV reactivation was observed in 17 of 45 (38%) high-risk patients with a median time to reactivation of 34 days. Acute GVHD was present in 7 patients on or about the time of CMV reactivation. There were no cases of CMV pneumonia and there was no CMV-associated mortality. Proved or probable invasive mold infections posttransplant, all caused by Aspergillus sp, were observed in 5 of 68 (7%) patients. Two patients died from Aspergillus infection: 1 while persistently neutropenic following graft failure, and 1 with fungal sinusitis.

The probabilities of grades II-IV and III-IV acute GVHD by day 200 were 34% and 6%, respectively (Figure 2A). There was no statistically significant difference in the probability of acute GVHD between patients who received 1 versus 2 doses of posttransplantation Cy. However, Figure 2B shows that the incidence of extensive cGVHD at 1 year in the group of patients who received 2 doses of posttransplantation Cy (5%) was suggestively lower than the incidence of extensive cGVHD in the group of patients who received 1 dose of posttransplantation Cy (25%; hazard ratio [HR] 0.21; 95% confidence interval [CI] 0.04-1.01; P = .05).

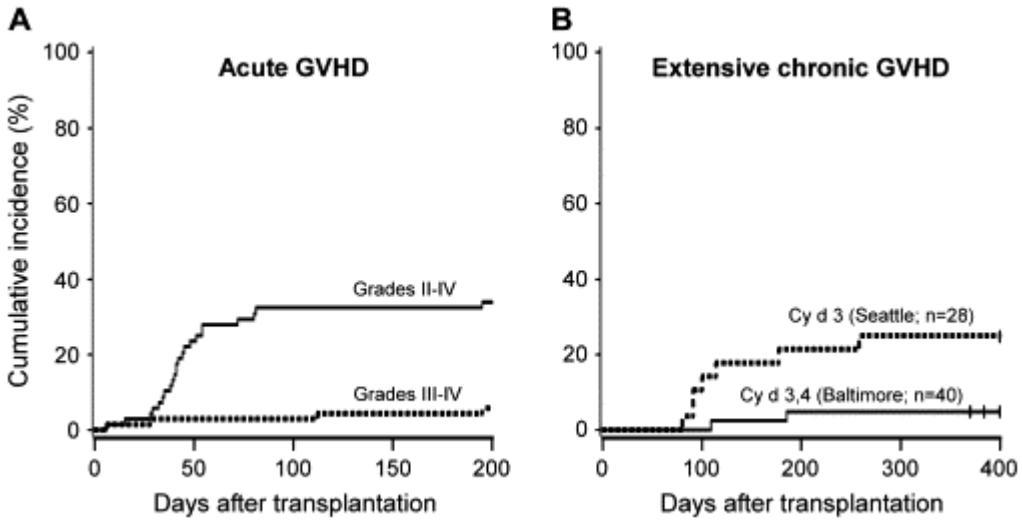

Figure 2. Cumulative incidence of aGVHD and cGVHD. (A) Cumulative incidence of aGVHD grades II-IV and III-IV. (B) Cumulative incidence of extensive cGVHD for patients who received 1 (Seattle) versus 2 (Baltimore).

The probabilities of NRM at 100 days and at 1 year after transplantation were 4% and 15%, respectively, and the probabilities of relapse at 1 and 2 years after transplantation were 51% and 58%, respectively (3A). There was no statistically significant effect of the dose of posttransplantation Cy on either NRM or relapse (data not shown). Patients with lymphoid malignancies had a significantly lower risk of relapse than patients with myeloid malignancies (HR 0.54, 95% CI 0.30-0.97, P = .04), suggesting efficacy of the GVL effect in patients with lymphoid malignancies.

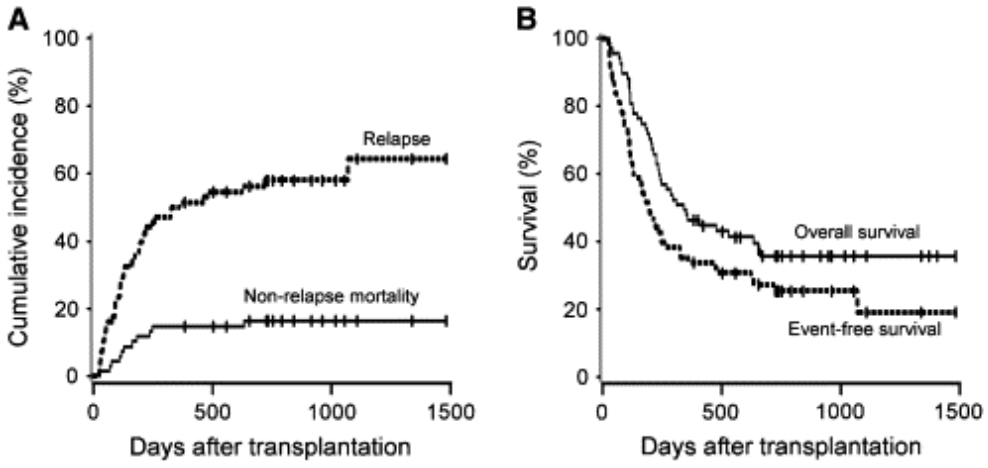

Figure 3. Outcomes among nonmyeloablative haploidentical BMT recipients. (A) Cumulative incidence of NRM and relapse. (B) OS and EFS. .doses of posttransplant Cy.

At a median follow-up among survivors of 745 days (range: 112-1483 days), the actuarial OS at 1 and at 2 years was 46% and 36%, respectively (Figure 3B). The actuarial EFS at 1 and at 2 years was 34% and 26%, respectively (Figure 3B). OS and EFS were not statistically significantly different between groups (data not shown). Causes of death included disease progression (n=31), GVHD (n=2), infection (n=4), and other causes (n=5).

Overall, 10 patients diagnosed with indolent or aggressive NHL were enrolled in these trials (O'Donnell P, 2007, Personal communications). Median number of prior regimens was 4 and four patients failed prior autologous HCT. Nine patients had sensitive disease to last chemotherapy regimen. Five patients had grade II acute GVHD and 4 patients had chronic GVHD. Four patients died with NRM at days 68, 109, 163, and 182, respectively. One patient relapsed at 89 and died from relapse at day 225. Five patients are living in remission after 683, 727, 735, and 923, and 1716 days, respectively.

Results from 21 patients diagnosed with HL and given nonmyeloablative HLA-haploidentical HCT were recently compared to those from 34 and 24 patients given HLA-matched related and unrelated nonmyeloablative HCT, respectively.{Burroughs, O'Donnell, et al. 2008 35218 /id} Fifty-two percent of haploidentical recipients had relapsed/refractory disease at time of HCT, which was higher than that among related recipients (21%) and comparable to the percentage among unrelated recipients (46%). Haploidentical recipients had median age of 31 years and 14% of patients had bulky disease, 62% had HCT-CI scores of ≥3, 57% had >5 prior regimens, 90% failed prior autologous HCT, and none of these characteristics differ from those among related or unrelated recipients. OS rate at 18-months among haploidentical recipients (71%) was comparable to that among unrelated recipients (74%) but superior to that among related recipients (47%, p=0.009). This was mainly due to exceptionally low cumulative incidences of NRM at 18 months among both haploidentical (5%) and unrelated recipients (8%) compared to that among related recipients (25%, p=0.02). Relapse rates were relatively high among the

three patient groups (39%, 56%, and 55%, respectively), which leaves room for improvement of relapse rate among haploidentical recipients by appropriate disease cytoreduction using autologous HCT since 76% of those patients had active disease at HCT.

Three patients aged, 56, 71, and 63 years old had diagnosis of MM and were given nonmyeloablative HLA-haploidentical HCT. Two post-HCT doses of cytoxan were given to the first two patients and only one dose to the third patient. Prior regimens were 3, 4, and 3, respectively. Only the third patient had failed prior autologous HCT. The first patient did not develop acute GVHD, while the last two had grade II acute GVHD. All three patients died from relapsed disease.

D. Rationale for including patients up to 75 years old

Until recently, patients over 60 years of age have not been considered eligible for more intensive therapies including autologous HCT. This is unfortunate since the median age of patients with NHL, MM, or CLL ranges between 60 and 70 years, [71,72] suggesting that the majority of those patients are excluded from curative treatment clinical trials. Limited data are available on the feasibility and efficacy of autologous HCT in patients above 60 years. Comorbidities are more common in elderly patients where individuals who are older than 65 years suffer on average from three different diseases. [73] Similarly, older cancer patients presented high levels of comorbidity. Comorbidities could be, in part, responsible for the poor tolerance of some elderly cancer patients to intensive therapies and the resultant relatively higher mortality compared to younger fit patients.

We have recently evaluated impact of comorbidities on outcomes of 273 patients diagnosed with NHL or HL and given autologous HCT. [54] Median age was 49 years with a range from 13 to 76. Comorbidities, as summarized by HCT-CI scores of >0, were found among 65% of patients, of whom 26% had scores of 3-4 and 4% scores ≥5. Several pretransplant risk factors were tested in Univariate and then multivariate analyses for their impacts on outcomes. Interestingly, only age ≥60 years and HCT-CI scores of ≥3 were associated with increased risk for NRM in Univariate analysis. However, when all factors were entered into a Cox regression model, age ≥60 years did not have a statistically significant impact on NRM (p=0.73) or OS (p=0.73), while comorbidities significantly impacted NRM (p=0.0009) and OS (p<0.0001). The non-significant impact of age persisted after resetting the age cut-off to ≥50 years. Patients with scores 3-4 and ≥5 had NRM of 15% and 42% and OS of 57% and 25%, respectively, compared to NRM of 3% and 8% and OS of 80% and 78% among patients with scores of 0 and 1-2, respectively. Of note, 8 patients in this cohort were aged >70years with upper limit of 76 years old and HCT-CI scores ranged between 0 and 4. Six of those patients received BEAM conditioning regimen, while the other two had radiolabeled monoclonal antibody-based therapy. Only one patient relapsed after 84 days and died from relapsed disease 445 days after his autologous HCT. Two patients died with NRM at 47 and 667 days post autologous HCT, respectively. Five patients are currently alive after a median follow up of 740 (range: 441-1187) days. These findings suggest that biological rather than chronological age should be considered for eligibility for autologous HCT.

Age per se does not seem to affect progenitor cell yield or success of mobilization in NHL or MM patients. [74-76] Several recent reports summarized outcomes of MM or NHL patients aged >60 years and given intensive chemo/radiotherapy and autologous HCT (Table 1). For NHL patients, NRM was in the range of 5-10%.[54] For MM patients, low incidences of NRM have been reported (range of 0-5%) even after melphalan of 200 mg/m^2. [76]

The use of nonmyeloablative conditioning before allogeneic HCT has extended the eligibility of this treatment option to patients above 60 years with relatively low NRM. Therefore, patients will be enrolled up to age 75 years and eligibility for HCT will be determined by health status and comorbidities.

Table 1: Autologous HCT in NHL and MM patients >60 years of age

Author	Diagnosis	No. of patients	Median age (range), years	Conditioning regimen	100-day NRM, %	Outcome
Moreau et al[77]	NHL	11	63 (61-65)	BEAM	0	OS 46%/3.5 years DFS 50%/3.5 years
Leger et al[78]	NHL	21	62 (60-73)	CBV BEAM	10	67% alive/19 months
Jantunen et al[75]	NHL	13	63 (60-70)	BEAM (9) BEAC (4)	8	Os 62%/16 months
Gopal et al[79]	NHL	53	62 (60-67)	BU-MEL-TT (24) TBI-CY-VP16 (16) TBI-CY (8)	9	OS 33%/4 years DFS 24%/4 years
Zallio et al[80]	NHL	13	67 (61-80)	MEL80 +/- MITOX	0	OS 59%/ 5 years
Bitran et al[81]	NHL	11	66 (65-78)	TBI-CY-VP16 (6) BEAM (5)	9	OS/DFS 44%/ 4 years
Villela et al[82]	NHL	13	63 (60-71)	BEAM CBV	0	Not stated
Jantunen et al[83]	NHL	88	63 (60-70)	BEAC (49) BEAM (34) TBI-CY (4)	11	OS 55%/5 years DFS 45%/ 5 years
Bouadi et al[84]	NHL	93	66 (60-76)	BEAC 29	5.4	Median OS 25 months DFS 38%/ 4 years
Palumbo et al[55]	MM	71	71 (55-75)	MEL100 x 2-3	0	CR 47% Median: OS = 56+ and DFS = 34 months
Sirohi et al[85]	MM	17	67 (65-74)	MEL200	17	CR 35% OS 3.6 years DFS 2 years
Badros et al[86]	MM	25 45	72 (70-82)	MEL200 MEL140	16 2	CR 20%, duration 31 months CR 28%, duration 15 months Overall OS 31% ± 10% Overall DFS 20% ± 9%
Reece et al[87]	MM	110	63 (60-73)	Heterogeneous	5	OS 39 months DFS 27 months
Jantunen et al[76]	MM	22	68 (65-73)	MEL200	0	CR 45% OS 57 months DFS 23 months

Abbreviations: BEAC=carmustine-etoposide-cytarabine-cyclophosphamide; CBV=cyclophosphamide-carmustine-etoposide; BU-MEL-TT=busulfan-melphalan-thiotepa; TBI-CY-VP16=total body irradiation-cyclophosphamide-etoposide; DLBCL=diffuse large B-cell lymphoma; EFS=event-free survival; FCL=follicular lymphoma; MCL=mantle cell lymphoma; MEL80=melphalan 80 mg/m2; MITOX=mitoxantrone.

4. Objectives

A. Proposal:

Patients with chemotherapy-resistant or bulky lymphoma, high-risk MM, or fludarabine-refractory CLL have limited curative treatment options. The use of GVL effects is one way of eradicating residual and chemotherapy-resistant disease. However, there are two potential problems. One is high NRM following conventional, myeloablative allogeneic HCT. The other is the unavailability of HLA-matched related or unrelated donors (for about 30% of patients) or the lack of time to identify unrelated donors due to rapid disease progression. Allogeneic HCT from HLA-haploidentical related donors following nonmyeloablative conditioning with 2 Gy TBI and fludarabine and post-transplantation immunosuppression with high dose Cy, tacrolimus, and thrice daily MMF was associated with acceptably low incidences of fatal graft rejection (2%), severe opportunistic infections (8%), severe acute GVHD (10%), and chronic extensive GVHD (22%) while allowing prompt engraftment (82%). However, relapse rates were 50% at 1 year resulting in 1 year EFS of 32%. We hypothesize that by applying a tandem approach of autologous high-dose HCT used for cytoreduction followed 40-120 days later by allogeneic nonmyeloablative HLA-haploidentical HCT, we can capture the benefits of high-dose autografting and HLA- haploidentical allografting (GVL effects). This approach would preserve the low GVHD and NRM observed after nonmyeloablative HLA-haploidentical HCT, while lowering the rate of relapse resulting in improved EFS.

B. Primary objectives

1. EFS at 1-year after autograft.

C. Secondary objectives

1. Relapse rates at 1-year after autograft.
2. OS at 1-year after autograft.
3. Incidence of grades II-IV acute GVHD and chronic extensive GVHD
4. NRM at 200 days and 1 year after allograft
5. Donor engraftment at day +84
6. Incidence of infections

5. Patient Selection

A. Inclusions:

1. Must have the capacity to give informed consent.
2. Detectable tumor prior to mobilization regimen
3. Age ≤75 years.
4. Patients with stored autologous stem cells will be allowed.
5. Stem cells from an identical donor could be used for autologous HCT
6. Marrow is the preferred source of stem cells from the HLA-haploidentical donor, however peripheral blood mononuclear cells (PBMC) could be used as stem cell source, **after clearance with the FHCRC principal investigator**, in the case of difficulties or contraindications to bone marrow harvest from the donor.
7. Cross-over to other tandem autologous-allogeneic research protocol (#1409 or other appropriate protocol) will be allowed if a suitable HLA-matched related or unrelated donor is identified before receiving the allogeneic transplantation and if the patient meets the eligibility criteria of the subsequent study.
8. Cross-over from other tandem autologous-allogeneic research protocol (#1409 or other appropriate protocol) will be allowed if the patient loses the suitable HLA-matched related or unrelated donor but has an available HLA-haploidentical donor before receiving the allogeneic transplantation and if the patient meets the eligibility criteria of the subsequent study.
9. The following disease diagnoses:

a. **Lymphoma:** Patients with

i. Diagnosis of NHL or HL, of any histological grade.

ii. Refractory or relapsed disease after standard chemotherapy.

iii. High risk of early relapse following autograft alone.

b. **Waldenstrom's Macroglobulinemia –** must have failed 2 courses of therapy

c. **CLL:**

i. Patients with either a

a) Diagnosis of T-cell CLL or T-cell PLL who have failed initial chemotherapy, patients with T cell CLL or PLL **or**

b) Diagnosis of B-cell CLL, B-cell small lymphocytic lymphoma, or B-cell CLL that progressed to prolymphocytic leukemia (PLL), who either:

I) Failed to meet NCI Working Group criteria[2] (**Appendix F**) for complete or partial response after therapy with a regimen containing fludarabine (or another nucleoside analog, e.g. 2-CDA, pentostatin) or experience disease relapse within 12 months after completing therapy with a regimen containing fludarabine (or another nucleoside analog).

II) Failed any aggressive chemotherapy regimen, such as FCR, at any time point.

III) Have "17p deletion" cytogenetic abnormality and relapsed at any time point after initial chemotherapy.

ii. Harvesting criteria for autologous HCT:

I) Previously collected PBMC may be used

II) Circulating CLL cells <5000

iii. Marrow involvement with CLL cells <50%

d. **MM**: Patients who

i. Have received induction therapy for a minimum of 4 cycles.

ii. In addition, patients **must meet at least one of the following criteria I-IX** (I-VII: at time of diagnosis or pre-autograft):

I) Any abnormal karyotype by *metaphase* analysis except for isolated t(11,14)

II) FISH translocation 4:14

III) FISH translocation 14:16

IV) FISH deletion 17p

V) β2-microglobulin > 5.5 mg/ml

VI) Cytogenetic hypodiploidy

VII) Plasmablastic morphology (≥2%)

VIII) Recurrent or non-responsive (less than PR) MM after at least two different lines of conventional chemotherapy.

IX) Progressive MM after a previous autograft (provided stored autologous CD34 cells are available)

e. **Plasma cell leukemia**: after induction chemotherapy

B. Exclusions:

1. Life expectancy severely limited by disease other than malignancy.
2. Seropositive for the human immunodeficiency virus.
3. Female patients who are pregnant or breastfeeding
4. Fertile men or women unwilling to use contraceptive techniques during and for 12 months following treatment.
5. CNS involvement with disease refractory to intrathecal chemotherapy.
6. 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.

7. Patients with fungal infection and radiological progression after receipt of amphotericin B or active triazole for greater than 1 month.
8. Patients with the following organ dysfunction:
    a. Cardiac: Symptomatic coronary artery disease or ejection fraction <40% or other cardiac failure requiring therapy (or, if unable to obtain ejection fraction, shortening fraction of < 26%). Ejection fraction is required if the patient has a history of anthracyclines or history of cardiac disease. Patients with a shortening fraction < 26% may be enrolled if approved by a cardiologist.
    b. Pulmonary:
        i. Corrected DLCO <50% of predicted, FEV1 <50% of predicted, and/or receiving supplementary continuous oxygen.
        ii. The FHCRC PI of the study must approve of enrollment of all patients with pulmonary nodules
    c. Liver function abnormalities: Patient with clinical or laboratory evidence of liver disease will be evaluated for the cause of liver disease, its clinical severity in terms of liver function, bridging fibrosis, and the degree of portal hypertension. The patient will be excluded if he/she is found to have fulminant liver failure, cirrhosis of the liver with evidence of portal hypertension, alcoholic hepatitis, esophageal varices, a history of bleeding esophageal varices, hepatic encephalopathy, uncorrectable hepatic synthetic dysfunction evinced by prolongation of the prothrombin time, ascites related to portal hypertension, bacterial or fungal liver abscess, biliary obstruction, chronic viral hepatitis with total serum bilirubin >3mg/dL, and symptomatic biliary disease.
    d. Karnofsky score <50% **(Appendix A)** for adult patients.
    e. Lansky Play-Performance score <40 **(Appendix B)** for pediatric patients.
    f. Patient with poorly controlled hypertension despite multiple antihypertensives.

6. **Donor Selection**

A. Inclusions:

1. Related donors who are genotypically identical for one HLA haplotype and who may be mismatched at the HLA-A, -B, -C or DRB1 loci of the unshared haplotype with the exception of single HLA-A, -B or –C allele mismatches.
2. Marrow is the preferred source of stem cells from the HLA-haploidentical donor, however PBMC could be used as stem cell source, **after clearance with the FHCRC principal investigator**, in the case of difficulties or contraindications to bone marrow harvest from the donor.
3. In the case that PBMC will be used as stem cell source, ability of donors < 18 years of age to undergo apheresis without use of a vascular access device; vein check must be performed and verified by an apheresis nurse prior to arrival at the SCCA
4. Age ≥ 12 years of age

B. Exclusions:

1. Donor-recipient pairs in which the HLA-mismatch is *only* in the HVG direction
2. Infection with HIV
3. Weight <20 kg.
4. A positive anti-donor cytotoxic crossmatch.

7. Evaluation and Counseling of Patient and Donor

A conference with the patient and family will be held to discuss this study and alternative treatments available for the treatment of lymphoma, MM, or CLL. The conferences will be conducted by the outpatient attending physician. All potential risks associated with the use of melphalan, Cy, TBI, BEAM, fludarabine, immunosuppressive drugs, and autologous and allogeneic transplantation should be discussed as objectively as possible to the patients or, in the case of minors, to the patient's responsible family members. It should be explained that patients offered this protocol have high-risk disease. Transplant-related risk of autologous and conventional allogeneic HCT for MM, lymphoma, or CLL; and poor disease control seen with non-myeloablative HCT without preceding cytoreduction should be described as the rationale for this trial.
Informed consent from the patient and the donor will be obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. A summary of the conference will be dictated for the medical record detailing what was covered.

8. Protocol Registration

A. FHCRC patients: Eligible patients will be identified by the Clinical Coordinators Office who will register the patient with the Registration Office (206-667-4728) between 8:30 am and 4:00 pm, Monday through Friday. After hours, the Registration Office can be reach by paging (206) 995-7437.

B. Collaborating institutions: Eligible patients will be identified by the principal investigator of the collaborating institution who will register the patient with the FHCRC Registration Office. Registration will include completion of the eligibility checklist/demographic form (Appendix J). This form and a copy of the signed informed consent will be faxed to (206-667-5378). Questions regarding eligibility or protocol information should be directed to Michelle Bouvier, R.N., Research Nurse (206-667-6993)

9. Plan of Treatment

A. Conventional Cytoreductive Therapy

Cytoreduction will be given to select patients with advanced disease prior to HCT to reduce tumor bulk. The need for cytoreductive therapy will be determined on clinical grounds by the attending physician and the principal investigator. Therapy may be given prior to arriving at the transplant center by the referring physician. Cytoreduction can be performed with any appropriate therapy for NHL, HL, Waldenstrom's Macroglobulinemia, CLL, MM, or plasma cell leukemia. The choice of therapy will depend on prior regimens and the current disease status and may be selected at the discretion of the attending physician and/or the referring physician. In general, cytoreductive therapy should be given to patients with bulky disease.

B. CNS prophylaxis

Patients at high risk for CNS disease will receive a diagnostic lumbar puncture per standard practice guidelines. Patients with history of CNS disease or positive lumbar puncture pre-transplant, will have instillation of IT MTX 12 mg on 2 occasions prior to transplant (between days -20 to -3) and 4-6 occasions after engraftment starting approximately day 32 and given every 14 days until completion. If the patient has an Ommaya Reservoir, the dose should be 6 mg. The IT MTX schedule can be individualized for patients at high risk of developing symptomatic leukoencephalopathy. For other drug information, see section# 11.

C. Ursodeoxycholic Acid Prophylaxis

Patients will receive ursodeoxycholic acid prophylaxis for hepatic complications per standard practice.

D. Autografting

1. Peripheral Blood Stem Cell (PBSC) mobilization

Patients may have autologous peripheral blood stem cells (PBSC) mobilized and stored prior to enrollment on this protocol. If previously stored PBSC are used on this protocol, patients proceed directly to autologous conditioning regimen 1 or 2 to be followed by autologous PBSCT. For patients without previously stored stem cells, autologous PBSC may be mobilized and collected according to available FHCRC or Outside Institution protocols (i.e. FHCRC 506), or on a treatment protocol at the discretion of the attending physician.

2. PBSC collection

The ***leukapheresis goal*** will be ***> 5x10^6 CD34$^+$ cells/kg. Transplant will NOT be carried out unless > 2.5 x 10^6 CD34$^+$ cells/kg are obtained***. The principle investigator should be consulted for recommendations if mobilization is inadequate.

At FHCRC, PBSC collections will be performed in the leukapheresis unit until the target dose of ***> 4x10^6 CD34$^+$ cells/kg*** has been collected and cryopreserved. Leukapheresis will begin 24 hours after the WBC recovers to 1,000/µl or by peripheral blood CD34 measurement of >10 x 10^6 CD34$^+$ cells/µl. Note that CD34 measurements more accurately correlate with higher CD34$^+$ cell collections at the time of leukapheresis than does the WBC and should be used if available. Collections will last approximately 2 hours using automated apheresis collection. PBSC will be cryopreserved using standard techniques. Follow standard practice guidelines for the platelet count prior to initiating leukapheresis.

3. Conditioning regimens

Conditioning chemotherapy for the autologous PBSC transplant is begun after recovery from mobilization/cytoreductive therapy. This should occur no earlier than 30 days following high dose mobilization regimens, but may occur earlier upon recovery from standard cytoreductive regimens. The conditioning regimen for the autologous PBSCT will consist of the following regimens:

1. Regimen 1: TBI 1200 cGy and Cyclophosphamide 120 mg/kg IV.
2. Regimen 2: BCNU 300 mg/m^2 IV, Etoposide 800 mg/m^2 IV, Ara-C 800 mg/m^2 IV, Melphalan 140 mg/m^2 IV.

*Patients with lymphoma, Waldenstrom's Macroglobulinemia, or CLL and no dose limiting radiation or significant comorbidities will receive Regimen 1. Others receive Regimen 2. Selection of the appropriate regimen is the discretion of the attending physician after discussing with the PI.

3. Regimen 3: Melphalan 200 mg/m^2
4. Regimen 4: Melphalan 140 mg/m^2

*Patients with multiple myeloma or plasma cell leukemia with no significant renal insufficiency or other significant comorbidities will receive Regimen 3. Others receive Regimen 4. Selection of the appropriate regimen is at the discretion of the attending physician after discussing with the PI.

a. Schedule for regimen 1: Cy/TBI

Table 2: Schedule for regimen 1: Cy/TBI

Treatment	Day							
	-7	-6	-5	-4	-3	-2	-1	0
Allopurinol (300 mg/m^2/po/day)	X	X	X	X	X	X	X	
Cyclophosphamide 60mg/kg		X	X					
Rest				X				
TBI 2.0 Gy BID					X	X	X	
PBSC infusion								X

i. Allopurinol: per standard practice guidelines

ii. Cyclophosphamide

Dosage: Administered at a dose of 60 mg/kg on two consecutive days, –6 and -5 of conditioning regimen, using standard practice guidelines for dosing weight. Total dose 120 mg/kg.

Supportive care: Use standard practice guidelines for supportive care

Mesna is the most effective agent for preventing cyclophosphamide urotoxicity by inactivating the alkylating metabolites in the urine. It dimerizes in serum to an inactive compound and does not inactivate hydroxycyclophosphamide in plasma. The dose will be 100% of cyclophosphamide dose given IV in 4 divided doses. Mesna will be given per institutional guidelines. In some cases, Mesna is not clinically indicated and patients instead will undergo bladder irrigation per institutional guidelines. Continuous bladder irrigation begins 1 hour before the first dose of cyclophosphamide and continues for 24 hours after the second dose.

For Other Drug Information, see section# 11.

iii. **Total body Irradiation:**

Total body irradiation (TBI), 200 cGy BID x 3 days is delivered from opposing Cobalt 60 sources or a linear accelerator at a dose rate of 6-15 cGy/min.

IV Hydration and Antiemetic Therapy: follow standard practice guidelines

b. **Schedule for regimen 2: BEAM (BCNU, Etoposide, Ara-C, and Mel)**

Table 3: Schedule for regimen 2: BEAM

Treatment	Day								
	-8	-7	-6	-5	-4	-3	-2	-1	0
Allopurinol (200 mg/m^2/po/day)	X	X	X	X	X	X	X	X	
BCNU 300 mg/m$_2$ IV x 1d		X							
Etoposide 100mg/m$_2$ IV BID x 4d			X	X	X	X			
Ara-C 100 mg/m$_2$ IV BID x 4d			X	X	X	X			
Melphalan 140 mg/m$_2$ IV x 1							X		
Rest								X	
PBSC infusion									X

i. Allopurinol: per standard practice guidelines

ii. BCNU (Carmustine):

Dosage: Carmustine 300 mg/m$_2$ IV x 1 will be infused over 3 hours on autografting day -7. **Carmustine should not be infused with solutions or tubing containing or previously containing bicarbonate solution.**

Administration: Carmustine is available as a sterile powder as 100 mg vials. The drug is reconstituted by dissolving the contents of the 100 mg vial in 3ml of sterile dehydrated (absolute) alcohol, followed by the addition of 27 mL of sterile water for injection. The resultant solution contains 3.3 mL of carmustine per mL of 10% alcohol. This solution may be further diluted with 0.9% sodium chloride or 5% dextrose injection to a final concentration of 0.2 mg/ml in glass containers. The manufacturer recommends that only glass containers be used for administration of this drug. Carmustine is rapidly degraded in aqueous solutions at a pH greater than 6. **Carmustine should not be admixed with nor administered through a common tubing or site with solutions containing sodium bicarbonate.**

Maintenance hydration: Follow standard practice guidelines.

iii. Etoposide (VP-16, Vepesid):
Dosage: Etoposide 100 mg/m^2 IV BID will be administered in 500-1000 cc normal saline over 2 hours on autografting days -6, -5, -4, and -3 for a total dose of 800 mg/m^2. **Etoposide may not be infused with sodium bicarbonate solutions.**

Availability, reconstitution and administration: Etoposide is commercially available in 100 mg/5 ml, 150 mg/7.5 ml, 500 mg/25 ml or 1000 mg/50 ml sterile multiple

dose vials. VP-16 should be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection, USP, to give a final concentration of 0.2 or 0.4 mg/ml. Precipitation may occur at solutions above 0.4 mg/ml concentration. It is recommended that VP-16 solution be administered IV over 2 hours. However, a longer duration of administration may be used when infusing large volumes of fluid. VP-16 should not be infused rapidly.

Supportive Care: Appropriate anti-emetics and sedatives should be given before the infusion begins. Before and 2 hours into the infusion, the patient is to receive 25 mg of diphenhydramine, and 100 mg of hydrocortisone to prevent allergic reactions. Normal saline plus 20 mEq KCL is to be continued at 2 liters/ m^2/day. If necessary, diuretics may be given. Since in rare cases metabolic acidosis has been observed after high dose VP-16, additional $NaHCO_3$ may be added to hydration, though not infused while VP-16 is infusing.
For Other Drug Information, see section# 11.

iv. Cytarabine(Ara-C):
Dosage: Cytarabine 100 mg/m^2
IV BID will be infused per standard practice guidelines on autografting days -6, -5, -4 and -3.

Availability and administration: Cytarabine is available in a reconstituted form in solutions containing 20, 50 and 100 mg of cytarabine per mL. These solutions have been reconstituted from a sterile powder with bacteriostatic water containing 0.945% benzyl alcohol for injection. The manufacturers state that the reconstituted solutions with water for injection may be diluted with 0.9% sodium chloride or 5% dextrose. The diluted solutions containing 0.5 mg of cytarabine per mL are stable for at least 8 days at room temperature.

For Other Drug Information: See section# 11.

v. Melphalan:
Dosage: Melphalan will be administered at a dose of 140 mg/m^2 IV x 1 infused over 30 minutes on autografting day -2.

Administration: Melphalan is available in 50 mg vials and when reconstituted with 10 mls sterile water results in a concentration of 5 mg/ml. The reconstituted melphalan is diluted in 250 cc normal saline to a concentration not greater than 0.5 mg/ml. Melphalan is administered per standard practice guidelines, not to exceed 60 minutes.

For Other Drug Information: See section# 11.

c. **Schedule for regimen 3: High-dose melphalan (200 mg/m^2 iv)**
High dose Melphalan will be given at least 30 days after using high dose cyclophosphamide for PBSC mobilization.

Table 4: Schedule for regimen 3: High-dose melphalan

Treatment	Days						
	-6	-5	-4	-3	-2	-1	0
Allopurinol (200 mg/m^2/po/day)			X	X	X	X	
Bactrim DS (1 tab po bid)	X	X	X	X	X		
Melphalan (adjust for GFR)					X		
PBSC infusion							X

i. Antiemetics: according to standard practice.
ii. Allopurinol: according to standard practice.
iii. Bactrim DS: according to standard practice

iv. Melphalan Administration:
Dosage: Melphalan will be administered at a dose of 200 mg/m^2 (adjust for GFR). This will be given in one dose infused on day -2. Dose will be calculated according to the institutional standard practice. The following dose adjustments will be required in patients with significant renal insufficiency:

GFR [mL/min]	**Melphalan dose**
≥40	100%
<40 or on hemodialysis	70%

Administration: High dose Melphalan is administered via a central catheter following reconstitution with the provided sterile diluent. High-dose melphalan can be administered undiluted as a bolus injection or diluted with sodium chloride and infused over 30 minutes.

Maintenance hydration**:** Per standard practice.

d. **Schedule for regimen 4: High-dose melphalan (140 mg/m^2 iv)**
Table 5: Schedule for regimen 4: High-dose melphalan

Treatment	Days						
	-6	-5	-4	-3	-2	-1	0
Allopurinol (200 mg/m^2/po/day)			X	X	X	X	
Bactrim DS (1 tab po bid)	X	X	X	X	X		
Melphalan (140 mg/m^2 iv)					X		
PBSC infusion							X

i. Antiemetics: according to standard practice.
ii. Allopurinol: according to standard practice.
iii. Bactrim DS: according to standard practice

iv. Melphalan Administration:
Dosage: Melphalan will be administered at a dose of 140 mg/m^2. This will be given in one dose infused on day -2. Dose will be calculated according to the institutional standard practice.

Administration: High dose Melphalan is administered via a central catheter following reconstitution with the provided sterile diluent. High-dose melphalan can be administered undiluted as a bolus injection or diluted with sodium chloride and infused over 30 minutes.

Maintenance hydration**:** Per standard practice.

4. PBSC Infusion

Infuse > 2.5 x 10^6 CD 34^+ cells/kg 36-48 hours after chemotherapy. See infusion guidelines, hydration requirements and pre-medication per institutional standard practice guidelines.

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5. Radiation Therapy

No radiation therapy is to be permitted concurrent with administration of melphalan. When blood count recovery is adequate (ANC >1000 /uL, platelets > 80,000/uL) after the autologous transplant, radiation may be administered for the following indications after consultation with the primary investigator and a radiation oncologist: (1) palliation of pain from bone lesions, (2) prevention of pathologic fractures, (3) relief of spinal cord compression or nerve root compression, (4) progression of solitary plasmacytomas of bone or solitary extramedullary plasmacytomas, or (5) bulky disease. A radiation oncology consultant in consultation with the attending physician will determine dose and duration of radiation to be administered. Radiation to the liver or lungs should be avoided.

6. Antibiotic Prophylaxis

a. All patients should receive prophylactic antibiotics when their granulocyte count is less than 500/mm^3. Refer to standard practice in Appendix C.

b. All patients should receive prophylactic Bactrim, Fluconazole and Acyclovir for prophylaxis against pneumocystis carinii pneumonia, systemic fungal infection, VZV and HSV, respectively. Refer to standard practice in Appendix C.

c. Patients shedding CMV will receive prophylactic Ganciclovir per standard practice in Appendix C.

7. Blood Products

Only irradiated blood products should be infused (RBC's and platelets). DO NOT IRRADIATE PERIPHERAL BLOOD STEM CELLS. CMV negative patients should receive only CMV negative or leukoreduced blood products.

E. Nonmyeloablative HLA-haplo-identical HCT

1. Pre-conditioning:

Upon recovery from autologous HCT, between 40-120 days post autografting (preferably within 60 days) patients will proceed to the nonmyeloablative allograft. If the interval exceeds 120 days, patients should be presented to PCC for discussion and approval.

"**Recovery" from autologous HCT** will be defined as follows:

a. Mucositis and gastrointestinal symptoms have resolved and TPN/ IV-hydration have been discontinued;
b. Steroid treatment for autologous GVHD has been discontinued;
c. LFTs, pulmonary and cardiac function are within the inclusion criteria for the initial autograft;
d. No evidence of radiological progression of previously documented fungal infections following treatment of amphotericin B or active triazole;
e. No detectable CMV-antigenemia;
f. Patients who experienced CMV-infection/reactivation following autografting: Ganciclovir or Foscarnet therapy has been completed more than two weeks ago and patient remains CMV-antigenemia negative (ID should be consulted if CMV-antigenemia persists);
g. Radiotherapy has been completed;

Any patient who does not fulfill these criteria may be discussed with the principle investigator for recommendations as to the timing of the allograft.

2. Venous access device:
A double-lumen central venous catheter will be required.

3. Conditioning regimen:
Treatment will be initiated in the outpatient department and patients will be admitted as medically necessary for control of transplant complications.

a. Outline of treatment plan (Scheduling is shown in Table 6A and 6B):
Note: Stem cell source will be marrow or PBMC with marrow being the preferred source.

Table 6A: Conditioning Schema and Immunosuppression Schedule for patients receiving marrow as source of stem cells	
Days –6, -5	Fludarabine 30 mg/m^2 iv qd Cyclophosphamide 14.5 mg/kg iv qd Mesna (dosed at 100% cyclophosphamide dose)
Days –4 to –2	Fludarabine 30 mg/m^2 iv qd
Day –1	200 cGy TBI at 6-7 cGy/min
Day 0	Infuse marrow allograft
Day +3	Cyclophosphamide 50 mg/kg (Must be administered 60-72 hr post-BMT) Mesna (100% cyclophosphamide dose)
Day +4	Begin Tacrolimus 1 mg IV and MMF 15 mg/kg po tid Begin G-CSF (5 µg/kg/d) IV or SC, continue until ANC>1000/mm^3 x 3d
Day +28	Assess chimerism in peripheral blood (T-cells and granulocytes)
Day +35	If no GVHD, discontinue MMF
Day +56	Assess chimerism in peripheral blood
Day +84	Assess disease status; assess chimerism in peripheral blood
Day +86	If no GVHD, start Tacrolimus taper
Days +180	Assess disease status, chimerism in peripheral blood If no GVHD, stop Tacrolimus
Days +360	Assess disease status, chimerism in peripheral blood

Table 6B: Conditioning Schema and Immunosuppression Schedule for patients receiving PBMC as source of stem cells	
Days –6, -5	Fludarabine 30 mg/m^2 iv qd Cyclophosphamide 14.5 mg/kg iv qd Mesna (dosed at 100% cyclophosphamide dose)
Days –4 to –2	Fludarabine 30 mg/m^2 iv qd
Day –1	200 cGy TBI at 6-7 cGy/min
Day 0	Infuse PBMC allograft
Days +3 and +4	Cyclophosphamide 50 mg/kg (first dose must be administered between 60-72 hr post-PMBC) (second dose administered approximately 24 hours after the first dose) Mesna (100% cyclophosphamide dose)
Day +5	Begin Tacrolimus 1 mg IV and MMF 15 mg/kg po tid Begin G-CSF (5 µg/kg/d) IV or SC, continue until ANC>1000/mm^3 x 3d
Day +28	Assess chimerism in peripheral blood (T-cells and granulocytes)
Day +35	If no GVHD, discontinue MMF
Day +56	Assess chimerism in peripheral blood
Day +84	Assess disease status; assess chimerism in peripheral blood
Day +86	If no GVHD, start Tacrolimus taper
Days +180	Assess disease status, chimerism in peripheral blood If no GVHD, stop Tacrolimus
Days +360	Assess disease status, chimerism in peripheral blood

b. Agent:

Menstruating female patients should be placed on an anti-ovulatory agent prior to initiating the conditioning regimen.

i. Fludarabine will be administered by IV infusion over 30 minutes on day-6 to day-2. The dose will be 30 mg/M2 with dose-reduction for decreased creatinine clearance*:

Fludarabine dosage should be reduced as follows:

C_{Cr} 46-60 ml/min, fludarabine = 24 mg/m^2
C_{Cr} 31-45 ml/min, fludarabine = 22.5 mg/m^2
C_{Cr} 21-30 ml/min, fludarabine = 19.5 mg/m^2
C_{Cr} <20 ml/min, fludarabine = 15 mg/m^2

*For adult patients, creatinine clearance may be estimated by the Cockcroft Formula:
C_{Cr} = (140 – age) x IBW (kg) x 0.85 (for women) P_{Cr} x 72
For pediatric patients, a formal measurement of creatinine clearance should be performed.

ii. Cyclophosphamide (14.5 mg/kg Adjusted BW*, unless IBW>ABW, then ABW per Standard Practice Guidelines) will be administered as an IV infusion over 1 hr on day -6 and day -5. Patients will be instructed to increase fluids overnight before cyclophosphamide administration. For pediatric patients, hydration will be given according to standard practice guidelines. For adult patients, hydration with normal saline at 3 cc/kg/hr iv will be started 2 hr prior to cyclophosphamide, then the rate will be reduced to 2 cc/kg/hr for 1 hr pre cyclophosphamide and continued for 8 hr post-cyclophosphamide. Mesna will be given in divided doses IV 30 min pre- and at 3, 6, and 8 hr post-cyclophosphamide. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of Mesna is equal to 100% of the total daily dose of cyclophosphamide. Urine output over 2 hr will be checked before administering cyclophosphamide and must be at least 3.0 cc/kg. Per standard practice guidelines, urine output must be maintained at 120mL over the first four hours post cyclophosphamide. Urine testing per institutional guidelines will be performed prior to administration of cyclophosphamide and on the day following cyclophosphamide to monitor for hematuria. Hemorrhagic cystitis is a known complication of high-dose cyclophosphamide therapy. **It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cy. This includes corticosteroids as anti-emetics.**

*Adjusted BW = [(ABW – IBW) 0.25] + IBW

iii. TBI (200 cGy) will be given on day –1 at a rate of 6-7 cGy/min per Standard Practice Guidelines.

4. Bone marrow infusion

All patients will receive infusion of a mononuclear cell (MNC) preparation of donor marrow on day 0. Red blood cell and plasma depletion will be done following the standard practice guidelines. Donor bone marrow will be harvested with a target yield of 4 x 10^8 nucleated cells/kg recipient IBW. The minimum acceptable yield should be 1 x 10^8 nucleated cells/kg recipient IBW. Yields of nucleated cells and MNC are about 25% and 85%, respectively. The CD34 and CD3 composition of allografts will be determined by flow cytometry.

5. **PBMC infusion**

Marrow is the preferred source of stem cells from the HLA-haploidentical donor, however PBMC could be used as stem cell source, **after clearance with the FHCRC principal investigator**, in the case of difficulties or contraindications to bone marrow harvest from the donor.

Donors who consent to PBMC donation will receive 5 daily doses of GCSF, 16 μg/kg/day by subcutaneous injection commencing on day –5. PBMC's will be collected in the afternoon of day -1, stored at 4C overnight, and infused as soon as possible on day 0. If the collection on day –1 contains less than 5.0 X 106 CD34+ cells per kg recipient weight, a second collection will be performed the following morning and transfused on day 0. Quantitation of CD34 and CD3 cells will be performed by the Cellular Therapy Lab. *For all patients, the target number of CD34 cells to be infused should be 5-6 X 106 cells per kg recipient weight.* PBSC in excess of 6.0 x 106 CD34 cells/kg recipient weight may be cryopreserved.

6. Post-transplant immunosuppression

a. Cyclophosphamide

i. For patients receiving marrow as stem cell graft: A single dose of cyclophosphamide [50mg/kg Adjusted BW*, unless IBW>ABW, then ABW per Standard Practice Guidelines] will be given on day +3 after transplant (within 60-72 hr of marrow infusion).
ii. For patients receiving PBMC as stem cell graft: Two doses of Cyclophosphamide [50mg/kg Adjusted BW*, unless IBW>ABW, then ABW per Standard Practice Guidelines] will be given on Day 3 post-transplant (between 60 and 72 hours after PBMC infusion) and on Day 4 posttransplant (approximately 24 hours after Day 3 cyclophosphamide).

Cyclophosphamide will be given as an IV infusion over 1 hr with Mesna and appropriate hydration as described above in Section 9D-3. Monitoring of urine output and for hematuria will be performed similarly. **It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cy. This includes corticosteroids as anti-emetics.**

b. Tacrolimus and MMF

i. Starting on day +4 (Day +5 for PBMC grafts), tacrolimus will be given at a dose of 0.03 mg/kg/d (for patients <30 kg) and 1mg/d (for patients >30kg) IV over 1-2 hr and should be changed to a PO dosing schedule as tolerated once a therapeutic level (5-15 ng/ml) is achieved. Serum levels of tacrolimus should be measured on day +8 and then weekly thereafter and the dose adjusted accordingly to maintain a level of 5-15 ng/ml.

Tacrolimus will be tapered after day +86 (adapted dose-reduction to be discontinued by day +180) if there is no evidence of GVHD.

ii. Starting on day +4 (day +5 for PBMC grafts), MMF will be given orally at a dose of 15 mg/kg tid. Doses will be rounded to the nearest 250 mg (capsules are 250 mg). If an observed toxicity related to MMF administration occurs in the clinical judgment of the investigator, the MMF dose will be adjusted. Based on previous observations in patients after nonmyeloablative HSCT, the side effect most likely to occur will be neutropenia due to myelosuppression. Severe gastrointestinal toxicity such as gastrointestinal hemorrhage

has been very rare after nonmyeloablative HSCT. A thorough evaluation of neutropenia should occur including peripheral blood chimerism studies, marrow aspiration and review of marrow suppressive medications (e.g. co-trimoxazole). Dose adjustments will not be made for neutropenia unless it is severe or persists after day +21. In the rare event of gastrointestinal toxicity that requires medical intervention including medication for control of persistent vomiting or diarrhea that is considered to be due to MMF, a 20% dose reduction will be made or the drug may be given IV at the same dose. For severe toxicity related to MMF (grade IV neutropenia refractory to G-CSF, severe refractory diarrhea, or overt gastrointestinal bleeding), the MMF may be temporarily stopped. MMF should be restarted at 20% reduced dose when the underlying toxicity subsides. The discontinuation of MMF at any point should be discussed with the Study PI and should be documented in the permanent medical record and all Case Report Forms (CRF).

MMF will be discontinued on day +35 if there is no GVHD.

7. Modification of immunosuppression for early disease progression or relapse

Guidelines provided in this section are for patients who demonstrate either (i) progression of stable disease present at the time of transplant or (ii) relapse of their underlying disease before discontinuation of immunosuppression has been completed. Significant *progression of disease* is defined in Table 7 below. *Relapse* is defined by presence of malignant cells in marrow, peripheral blood or extramedullary sites detectable by morphologic, flow cytometric, cytogenetic or molecular assays not evident at the time of transplant. Patients fulfilling these criteria should undergo a reduction in immunosuppression after careful evaluation for GVHD. In the event that patients with early disease progression or relapse do not have GVHD, immunosuppression should be discontinued. Persistence of stable, underlying disease itself does not mandate accelerated reduction of immunosuppression.

Table 7 Definition of disease progression

Disease	Signs of Progression
MM or plasma cell leukemia	• Increasing bone pain or • increase in serum/urine monoclonal protein by 25% or • Increase in circulating or bone marrow blasts by 25%
Waldenstrom's Macroglobulinemia	• new sites of lymphadenopathy or • increase of ≥ 25% in lymph node size (assessed by CT scan) or • blood or bone marrow involvement with clonal B cells (lymphoma) or • increase of ≥ 25% bone marrow involvement or • increase in serum/urine monoclonal protein by 25%
CLL, NHL, HL	• new sites of lymphadenopathy or • increase of ≥ 25% in lymph node size (assessed by CT scan) or • blood or bone marrow involvement with clonal B cells (lymphoma) or • increase of ≥ 25% bone marrow involvement or • increase of ≥ 25% blood involvement (of lymphocyte count > $50x10^3/\mu l$) with clonal B-cells (CLL)

If there is no disease response 4 weeks after stopping immunosuppression and GVHD has not developed, patients may be considered for DLI (which is not part of this protocol) and further therapy as per institutional protocols for disease relapse or progression after allogeneic HCT.

Patients deemed to be at high risk for graft rejection based on low donor chimerism may also be eligible for DLI (which is not part of this protocol) or a second allogeneic HCT on other protocols. In the setting of low donor chimerism *without* evidence of disease progression, immunosuppression should be continued at full dose so that DLI on other protocols can be considered.

8. Growth Factor Support

Patients will receive G-CSF at 5 μg/kg/d [rounded to the nearest vial size (300 μg or 480 μg)] IV or SC starting at day +4 (Day +5 for PBMC grafts), and continuing until the ANC >1000/mm^3 for 3 d.

9. Infection prophylaxis and therapy

Patients will receive prophylaxis and therapy for bacterial, fungal and viral infections according to Standard Practice Guidelines. Standard CMV monitoring and prophylaxis should commence at the time of transplant and should continue as appropriate. Please see standard practice per Appendix C

10. Evaluation

NOTE: Research blood specimens marked by ** should NOT be drawn until AFTER the patient and donor have signed the consent forms for protocol 2241.

A. HLA-typing of patient and potential donors (pre-transplant evaluation)

1. As broad a range of potential related donors as possible should be typed. Included are parents, siblings, eligible children, and cousins.
2. Serotyping (HLA-A, B, C) and DNA typing (HLA-A, B, C, DRB1, DQB1) of patient and donor will be performed.
3. Leukocyte and/or florescence activated cell sorter cross match between the patient and donor will be done. Recipient must have a negative cytotoxic cross-match to donor lymphocytes, otherwise an alternative HLA-haploidentical donor must be identified.
4. KIR genotype will not be used in determining donor selection.
5. Blood samples for HLA-typing should be sent to: Clinical Immunogenetics Lab for HLA-typing (heparinized green top tube, 10 cc), 206-667-7700; SCCA G7-200.

B. Donor:

Donors will be evaluated according to Standard Practice Guidelines and should include

1. Complete history and physical examination.
2. Lab and research tests
   a. **CBC with differential including platelet count and reticulocytes on day –2** (pre-marrow harvest or PBMC collection) and **day 0** (day of marrow harvest or PBMC collection).
   b. **Chemistry panel**
   c. **Hepatitis screen, CMV, syphilis, HIV and HTLV I serology**
   d. **ABO Rh blood typing**. If the donor has antibodies against the red cells of the recipient or vice versa, the titers must be determined. Cross-matching between patient and donor (Clinical Immunogenetics Lab) will be performed. Appropriate RBC depletion of the marrow allograft, in case of presence of donor ant-recipient antibodies, will need to be done per standard procedures.
   e. A heparinized blood sample (green top tube, 10 cc) as a donor reference for subsequent determination of **donor chimerism** should be sent to the Cytogenetics Lab if the donor-recipient pair is sex-mismatched or to the Clinical Immunogenetics Lab if sex-matched. Label "Protocol 2241".
   f. In the case that PBMC will be used as stem cell source, ability of donors < 18 years of age to undergo apheresis without use of a vascular access device; vein check must be performed and verified by an apheresis nurse prior to arrival at the SCCA. Please note donors ≤12 years of age are not eligible for the study.

C. Patient:

1. **Pre-mobilization Evaluation-**Patients will be evaluated with standard work up and standard disease specific staging

2. **Autografting Evaluations (This is a recommended evaluation schedule. Tests should be done within 30 days of auto graft).**
   a. Pre-autografting per Standard Practice or standard practice guidelines of your institution. In addition, obtain the following
      i. ECG (if not already done within 30 days of planned autologous transplant)

ii. Pulmonary function tests for patients ≥6 with corrected DLCO (Note: for patients who show <60% carbon monoxide diffusion capacity, or if otherwise clinically indicated, arterial blood gases should be obtained)
iii. For patients with abnormal cardiac exam, or symptoms suggestive of CHF, or history of anthracycline exposure obtain Echocardiogram or MUGA to calculate ejection fraction
iv. Lumbar puncture for patient's at risk for CNS involvement per Standard Practice, see Appendix L
v. Assessment of patient pretransplant comorbidities and assigning scores using the HCT Comorbidity Index (HCT-CI; see Appendix N).
vi. **Additionally, see the following tables (Tables 8 and 9) for disease specific pre-transplant evaluations.**

Table 8: Disease-Specific Pre-Auto and Pre-Allo Evaluations for CLL, HL, NHL

Note: All bone marrow aspirates and biopsies are **bilateral pre-auto** and we recommend them to be collected within **30 days** of treatment. If Pre-Auto bone marrow is positive for disease involvement, then pre-allo bone marrow should be bilateral. See Tables 9 and 10 for post-transplant evaluations and additional lab instructions.

Specimen / Test / Imaging	Clinical / Research	Comment
Bone marrow aspirate		
Pathology	Clinical	
Flow Cytometry- *see comment	Clinical	*No HL *Include CD38 expression for CLL
Cytogenetics	Clinical	
FISH for clonal abnormalities	Clinical	*If previously abnormal
PCR for t(11:14) - *see comment	Clinical	*Mantle Cell NHL only and pre-auto only
PCR for t(14:18) - *see comment	Clinical	*Follicular NHL only, and pre-auto only
Bone marrow biopsy		
Pathology- *see comment	Clinical	*HL – only if history of BM involvement
Peripheral Blood		
Storage for chimerism analysis	Clinical	
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 9: Disease-Specific Pre-Auto and Pre-Allo Evaluations for MM, Waldenstrom's Macroglobulinemia, or plasma cell leukemia

Note: All bone marrow aspirates and biopsies are **bilateral pre-auto** and we recommend them to be collected within **30 days** of treatment. If pre-auto bone marrow is positive for disease involvement, then pre-allo bone marrow should be bilateral.
See Tables 10 and 11 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	
Bone marrow biopsy		
Pathology	Clinical	
Peripheral Blood		
Storage for chimerism analysis	Clinical	
SPEP/IFIX	Clinical	
Quantitative Ig levels	Clinical	
β-2 microglobulin	Clinical	
LDH	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 and serum creatinine on day of creatinine clearance)	Clinical	
Bence Jones quantification and serum free light chain assay - *see comment	Clinical	*FLC for patients with light chain disease only
Imaging		
MRI – *see comment	Clinical	*MM or plasma cell leukemia only, and only Pre-Auto
Skeletal survey – *see comment	Clinical	*MM or plasma cell leukemia only
CT of chest, abdomen, pelvis (neck if indicated) – *see comment	Clinical	*Waldenstrom's Macroglobulinemia only

3. Post-Autograft Evaluation

Post-autografting workup is to be performed according to institutional Standard Practice guidelines. If 90 days passed after the auto-graft, the patient should undergo all evaluation guidelines detailed under the Pre-Allograft Evaluation (next section).

4. Pre-Allograft Evaluation

The routine pre-allografting workup is to be performed according to institutional Standard Practice and is to include the following:

i. History: A complete history with full details of the patient's prior treatment and response.

ii. Careful physical exam with determination of Karnofsky score (**Appendix A**) or Lansky Play score (**Appendix B**) and findings related to underlying malignancy.

iii. Assessment of patient pretransplant comorbidities and assigning scores using the HCT Comorbidity Index (HCT-CI; see Appendix N).

iv. Chest X-ray (PA and lateral views).

v. In preparation of posttransplant chimerism analysis, heparinized peripheral blood from patient and donor will be drawn and sent to: Clinical Immunogenetics Lab (For FHCRC patients send to G-7107) for VNTR-based chimerism analysis for *sex-matched and sex-mismatched transplants*. Label "Protocol 2241". Pretransplant samples are to be sent to allow storage of DNA for evaluation of post-transplant chimerism.

vi. Additionally, see above tables 8 and 9 for disease specific pre-transplant evaluations.

5. Post-allograft Evaluation

See Table 10 for disease specific post-transplant evaluation on Day +28, 56, 84, etc. This is a recommended evaluation schedule.

Additionally, include the following for all diseases:

i. CBC three times a week, or more often if clinically indicated, from day 0 until day +28, and twice weekly until 2 months post-transplant or later if clinically indicated.

ii. Electrolyte panel, renal and hepatic function three times a week until day 28 and then once per week until tacrolimus is stopped, unless clinical circumstances suggest the need for more frequent evaluations.

iii. Patients should be assessed for the need of bisphosphonates and IVIG monitoring and replacement therapy per Institutional Guidelines

Patients with MM: Patients should be assessed for the need of bisphosphonates per Institutional Guidelines".

Assessment of GVHD:

i. Patients will be followed closely for signs and symptoms of acute or chronic GVHD as outlined in **Appendices D and E,** respectively. Skin involvement should be assessed by punch biopsy. The percentage of body surface area involved will be recorded. GI symptoms suspicious for GVHD should be evaluated by endoscopy and biopsy as indicated. Time to onset of GVHD will be recorded.

ii. First-line therapy will be reinstitution of tacrolimus, if previously discontinued, and administration of high-dose corticosteroids with subsequent taper as described in the Standard Practice Guidelines. Patients with GVHD who are steroid-refractory may be eligible for treatment protocols for acute or chronic GVHD or conventional salvage therapy.

Non-relapse mortality:

i. Every effort will be made to determine the exact cause of death for all patients as they occur. Non-relapse-related mortality, regardless of cause, occurring by day +200, will be recorded and reported on CRFs.

Post-allograft day +84 Evaluation.

These patients should be followed as standard allograft recipients. The following evaluations should be obtained:

Chronic GVHD workup (see Appendix E)

i. A complete history with full details of the patient's prior treatment including dates immunosuppression stopped and response.
ii. Physical examination with determination of Karnofsky score and attention to presence of GVHD (skin, oral, scalp, and body hair distribution, nails, icterus, etc).
iii. Skin biopsy.
iv. Schirmer's Tear test.
v. Pulmonary function test.
vi. PA and Lateral Chest X-ray.
vii. Dietician departure assessment.
viii. Gynecological departure assessment (adult female).

Table 10: Protocol 2241: Post-Allogeneic Transplant Evaluation

This is a recommended evaluation schedule. See text and additional table for pre-transplant evaluation and lab information

Disease	Specimen/ Test/ Imaging	Clinical/ Research	Comment	Days				Years		Annual x 5 years
				28	56	84	180	1	1.5	
CLL	**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						
	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	*See comment	*See comment
	β-2 microglobulins	Clinical	*If abnormal pre-transplant			*See comment				
	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	
HL – No 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		
	Cytogenetics	Clinical	*If abnormal pre-transplant			*See comment		*See comment		
	FISH	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						
	Quantitative Ig Levels	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	LDH	Clinical				x	x	x	x	x
	Imaging									
	CT of chest, abdomen, pelvis (neck if indicated)	Clinical	*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	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	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						
	Quantitative Ig Levels	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	LDH	Clinical				x	x	x	x	x
	Imaging									
	CT of chest, abdomen, pelvis (neck if indicated)	Clinical	*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 *** 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	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						
	Flow cytometry	Clinical	*If abnormal 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	*See comment	*See comment
	LDH	Clinical				x	x	x	x	x
	Imaging									
	CT of chest, abdomen, pelvis (neck if indicated)	Clinical	*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 AND bone marrow not done	*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 AND bone marrow not done	*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 and Plasma Cell Leukemia	**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	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						
	Quantitative Ig Levels	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	SPEP and IFIX	Clinical				x	x	x	x	x
	β-2 microglobulins	Clinical				x	x	x	x	x
	Cryoglobulins, c-reactive protein, serum viscosity	Clinical				x	x	x		x
	24 Hour Urine									
	Creatinine clearance/protein excretion	Clinical	*If abnormal pre-transplant			*See comment	*See comment	x	*See comment	*See comment
	UPEP and IFIX	Clinical	*If abnormal pre-transplant			*See comment	*See comment	x	*See comment	*See comment
	Imaging									
	Skeletal survey (including skull and long bones)	Clinical						x		x
	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	**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	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						
	Quantitative Ig Levels	Clinical	*If abnormal pre-transplant	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment	*See comment
	SPEP and IFIX	Clinical				x	x	x	x	x
	β-2 microglobulins	Clinical				x	x	x	x	x
	Cryoglobulins, c-reactive protein, serum viscosity	Clinical				x	x	x		x
	24 Hour Urine									
	Creatinine clearance/protein excretion	Clinical	*If abnormal pre-transplant			*See comment	*See comment	x	*See comment	*See comment
	UPEP and IFIX	Clinical	*If abnormal pre-transplant			*See comment	*See comment	x	*See comment	*See comment
	Imaging									
	CT of chest, abdomen, pelvis (neck if indicated)	Clinical	*If abnormal pre-transplant		*See comment	x	x	x	x	x
	GVHD evaluation	Clinical	See text for details			x				

Table 11: Additional Lab Instructions

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 identified otherwise.

Off-site providers may use local facilities for the tests.
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) 288-7700
Pathology (*aspirate*)	Clinical	2mL bone marrow in EDTA/ formalin	SCCA Pathology Lab	Seattle Cancer Care Alliance (206) 288-1355
Pathology (*biopsy*)	Clinical	1cm bone marrow in formalin **OR** mounted in paraffin	SCCA Pathology Lab	Seattle Cancer Care Alliance (206) 288-1355
Flow Cytometry	Clinical	2mL bone marrow in green-top tube	UW Hematopathology Lab	Seattle Cancer Care Alliance (206) 288-7060
Cytogenetics	Clinical	3mL bone marrow in green-top tube	SCCA Cytogenetics Lab	Seattle Cancer Care Alliance (206) 288-1390
FISH	Clinical	2mL bone marrow in green-top tube	SCCA Cytogenetics Lab	Seattle Cancer Care Alliance (206) 288-1390
PCR for 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) 288-7060
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) 288-7060
Flow Cytometry	Clinical	10mL blood in green-top tube	UW Hematopathology Lab	Seattle Cancer Care Alliance (206) 288-7060
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) 288-2057
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) 288-2057
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) 288-7060
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) 288-7060

Outside institutions may use VNTR analysis (sex- matched transplants) or sex chromosome FISH-analysis (sex-mismatched transplants) for chimerism analysis.

11. Irradiation and Marrow Administration - Toxicities and Complications

A. Total Body Irradiation: TBI will be given in one 2.0 Gy fraction at a rate of 6-7 cGy/min. Dosimetry calculations are performed by the radiation therapist. Refer to Standard Practice of the institution for information regarding administration, toxicity and complications.

B. Fludarabine:

1. Description: Fludarabine monophosphate is a purine antimetabolite that, after administration, undergoes rapid conversion in plasma to the nucleoside 2-fluoro ara-A (F-araA). F-araA subsequently enters cells where it is phosphorylated to F-araATP and the monophosphate F-araAMP. Once activated, F-araATP inhibits DNA polymerase and ribonucleotide reductase. The monophosphate F-araAMP, once incorporated into DNA, is an effective DNA chain terminator. Following IV administration, the drug is metabolized to 2-F-araA and widely distributed in tissues. 2-F-araA is excreted primarily in urine and has a terminal elimination half-life of 7-12 hr.

2. Storage and Administration: Fludarabine monophosphate is commercially available as a 50 mg/vial which is reconstituted with 2 ml of sterile water, resulting in a 25mg/ml solution. The desired dose is further diluted to concentrations of 0.04-1 mg/ml in normal saline or 5% dextrose (50-100ml) for injection and will be administered by IV infusion over 30 minutes or longer. Fludarabine will be administered by IV infusion over 1 hr in a dose of 30 mg/m^2/day on days -6 to -2.

3. Side Effects and Toxicity: Clinical toxicities of fludarabine monophosphate include: myelosuppression, primarily lymphopenia and granulocytopenia, alopecia, rash, dermatitis, nausea, vomiting, anorexia, stomatitis, diarrhea, somnolence, fatigue, peripheral neuropathy, mental status changes, cortical blindness, hepatocellular toxicity with elevation in serum transaminases, and interstitial pneumonitis. These effects are reversible when the drug is discontinued. Immunosuppression observed with the use of fludarabine increases the risk of infection which can be life-threatening

C. Cyclophosphamide:

1. Description: Cyclophosphamide is an alkylating agent which prevents cell division primarily by cross-linking DNA strands. Cyclophosphamide is cell cycle non-specific. Cyclophosphamide is not stem cell toxic.

2. Storage and Administration: Cyclophosphamide for injection is commercially available in 2000 mg vials which are reconstituted with 100 ml sterile water for injection. The concentration of the reconstituted product is 20 mg/ml. The calculated dose will be diluted further in 250-500 ml of Dextrose 5% in water. Each dose will be infused over 1-2 hr (depending on the total volume). **It is crucial that no immunosuppressive agents are given until 24 hours after the completion of the post-transplant Cy. This includes corticosteroids as anti-emetics.**

3. Side Effects and Toxicity: Clinical toxicities of cyclophosphamide include alopecia, nausea and vomiting, headache and dizziness, hemorrhagic cystitis, cardiotoxicity, immunosuppression, myelosuppression, pulmonary fibrosis, increased hepatic enzymes and syndrome of inappropriate anti-diuretic hormone (SIADH).

D. Mesna

1. Description: Mesna is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxazaphosphorines (cyclophosphamide and ifosfamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy. Mesna binds with acrolein, the neurotoxic metabolite produced by the oxazaphosphorines, to produce a non-toxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxazaphosphorines.

2. Storage and Administration: Mesna is commercially available in 200 mg, 400 mg and 1000 mg vials containing a 100 mg/ml solution. Each dose of mesna will be diluted further in 50 ml of normal saline to be infused over 15 min. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of mesna is equal to 80% of the total daily dose of cyclophosphamide.

3. Side Effects and Toxicity: At the doses used for uroprotection mesna is virtually non-toxic. However, adverse effects which may be attributable to mesna include nausea and vomiting, diarrhea, abdominal pain, altered taste, rash, urticaria, headache, joint or limb pain, hypotension and fatigue.

E. Tacrolimus

1. Description: Tacrolimus, also known as FK-506, is a macrolide immunosuppressive agent. Tacrolimus inhibits lymphocytes by forming a complex with FKBP-12, calcium, and calmodulin, leading to the decrease in the phosphatase activity of calcineurin. Calcineurin mediates the first intracellular signal required for T-cell activation after antigen recognition by the T-cell receptor. This drug is used with corticosteroids for prophylaxis of organ rejection in patients receiving allogeneic liver transplants and for prophylaxis of GVHD in the setting of HSCT. It is also used for immunosuppression after kidney, cardiac, pancreas, pancreatic islet cell and small bowel transplantation. This drug is well-absorbed orally. It is metabolized in the liver by unknown mechanisms, but demethylation and hydroxylation have been proposed based on *in vitro* studies. The metabolized products are excreted in the urine.

2. Storage and Administration: Tacrolimus is commercially available in capsule form (0.5, 1.0 and 5.0 mg) and as a sterile solution in 1 mL ampules (5 mg/mL) for IV administration.

3. Side Effects and Toxicity: Adverse reactions include tremor, headache, insomnia, nausea, diarrhea, hypertension, and renal dysfunction (hyperkalemia, increased BUN and creatinine).

Drugs that may increase blood levels of tacrolimus include: macrolide antibiotics, antifungals (fluconazole and itraconazole), calcium channel blockers, cimetidine, danazol, methylprednisolone and metoclopramide. Drugs that may decrease blood levels of tacrolimus include: phenobarbital, phenytoin, carbamazepine, rifamycins and the anti-fungal agent caspofungin.

F. Mycophenolate Mofetil

1. Description: Mycophenolate Mofetil is the morpholinyl ethyl ester prodrug of the active immunosuppressant mycophenolic acid (MPA). This active metabolite is a noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase, particularly the type II isoform that is more prominent in activated lymphocytes. As a result of the inhibition of de novo purine synthesis, proliferation of T- and B-lymphocytes is blocked and antibody production is inhibited. There are no pharmacokinetic interactions with ganciclovir, cotrimoxazole, oral contraceptives or cyclosporine.

2. Storage and Administration: MMF is commercially available in an oral and an intravenous formulation. The oral formulation is supplied in 250mg hard gelatin capsules and can be stored at room temperature. MMF for i.v. administration is supplied as a lyophilized powder in a glass vial containing the equivalent of 500mg.

3. Side effects and toxicity: Side effect profiles include diarrhea, leukopenia, sepsis, allergic reactions, and vomiting. An increase in certain types of infection mainly from the herpes virus family (CMV, HSV & VZV) and candida has been reported. 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, and on one occasion bloody 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). Dose adjustments are described in section 9E.6.h. With the exception of hypophosphatemia there seems to be no difference in side effects between i.v. and oral MMF administration and efficacy is the same with both administration routes.

G. Marrow or PBMC infusion

Refer to Standard Practice Guidelines.

H. Graft-versus-host disease (GVHD)

The major toxicity of T-replete HSCT from related, HLA-haploidentical donors is GVHD. In the Phase II trial of cyclophosphamide-induced immunosuppression discussed above in Section 3 (Preliminary Results), cumulative incidence of grade II and grades III-IV GVHD were ─ and 10%, respectively. Chronic extensive GVHD was observed in 22% of patients. Mortality secondary to complications of GVHD therapy was 1/5 patients. Using thrice weekly MMF and prolonging the course of tacrolimus in addition to postgrafting cyclophosphamide have resulted in these relatively low rates of the clinically significant GVHD.

***Diagnosis*:** Skin involvement will be assessed by biopsy with percentage of body surface area involved recorded. GI symptoms suspicious for GVHD will be evaluated by biopsy as indicated. Acute and chronic GVHD will be graded according to established criteria (Appendices D and E).

12. Protocol Registration and Special Considerations

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex / Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	11	17	28
Ethnic Category Total of All	12	18	30
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific	0	0	0
Black or African American	0	1	1
White	11	16	27
Racial Categories: Total of All	12	18	30

13. Guidelines for Serious Adverse Event Reporting

A. Monitoring the progress of trials and the safety of participants

Protocol 2241 will become a multi-institutional clinical trial that is monitored by the principal investigator (PI), Dr. Mohamed Sorror, with oversight by a Data Safety and Monitoring Board (DSMB), the Data and Safety Monitoring Committee (DSMC) and the Institutional Review Board (IRB). The PI reviews outcome data for each individual patient at a minimum of 3 months after HSCT and the updated data are presented at Mixed Chimerism Meetings (includes co-investigators).

Serious adverse events are reported to the trial coordinator, the study nurse or directly to the PI. The trial coordinators at collaborating centers or the local PIs will fax an official report of a serious adverse event to the coordinating center (FHCRC) within ten days. The serious adverse event report is reviewed by Dr. Sorror. If the serious adverse event meets the FHCRC criteria for reporting then an official signed report is submitted to the FHCRC Institutional Review Office (IRO). All deaths, regardless of the cause, are reported to the IRB. Protocol 2241 has a DSMB responsible for monitoring patient safety on this clinical trial. The DSMB meets twice a year and all outcome data is reviewed including all adverse events reported to the coordinating center (FHCRC) along with those officially reported to the FHCRC IRO. The DSMB confirms that the trial has met not any stopping rules and reviews any patient safety problems necessitating discontinuation of the trial. A report from the DSMB is submitted to the FHCRC

IRB as well as the trial coordinators/local PIs of this protocol. The DSMB will discontinue the review of outcomes when this protocol is closed to accrual. Furthermore, the FHCRC also has a DSMC that reviews the progress of the protocol with respect to the monitoring plan at the time of each annual renewal. As with initial review, annual IRB review and approval is also required.

With respect to safety, patients are monitored for the development of graft versus host disease (GVHD), myelosuppression and infections. All patients, regardless of diagnosis, will be considered in the safety analysis. Because of the older age profile of the patients, complications of HSCT and donor lymphocyte infusions (DLI), primarily GVHD and infections, may be more severe than usually encountered. These events will be closely monitored and severity of GVHD graded. Formal stopping rules are provided. Transplant-related mortality (TRM), defined as death before day 100 not related to progression of disease, will be closely monitored. This endpoint encompasses serious problems associated with the potential complications of severe GVHD, infections and rejection.

Flow of information concerning clinical trial participants originates with the clinicians and nurses in the clinic or referring clinicians at other institutions and is transmitted to the trial coordinator. At the FHCRC, health care providers and rotating attending physicians assess patients and record their observations regarding toxicity and response outcomes in the medical record. This documentation is extracted by the study nurse within 140 days +/- after HCT via chart review and collection of copies of source documents and entered into a hard copy or electronic Case Report Form (CRF). Thus, multiple health care providers provide independent observations and participate in monitoring this trial. The PI may be a clinician for some patients entered on this trial. However, assessments are the sum total of the primary health care provider (fellow or physician assistant), floor or outpatient nurse and the PI or other attending clinician involved with the patient averting possible conflict of interest having the PI as the attending clinician for protocol patients. If determination of adverse events is controversial, co-investigators will convene on an ad hoc basis as necessary to review the primary data and render a decision.

B. Plans for assuring compliance with requirements regarding the reporting of adverse events

The adverse event reporting in this multi-institution clinical trial will follow an adapted version of the FHCRC Guidelines for serious adverse event (SAE) reporting. These guidelines detail the expedited reporting requirements, definitions of particular events. All SAEs that meet expedited reporting are reported to the IRO within 10 days of the investigator, trial coordinator, or research nurse upon learning of the event. A completed SAE report form, signed by the PI, must be received by the IRO within 10 calendar days. Only toxicities that meet the criteria for an SAE will be collected and reported. For patients being cared for at the FHCRC, health care providers communicate with the PI, trial coordinator or research nurses as events occur triggering subsequent reporting. For patients not being cared for at FHCRC the outside facilities communicate with the PI, trial coordinator, or research nurse for these reporting purposes. All other deaths and expected serious adverse events are reported to the IRB at the time of annual renewal and at the biannual mixed chimerism meeting. The PI for a study is responsible for this reporting and the IRO assures adverse event reporting on an annual basis. The PI in the annual application for grant continuation will summarize reports of toxicities. Furthermore, an additional safeguard for adverse event analysis and reporting in this protocol is provided by stopping rules and interim analysis. All collaborating PIs have fulfilled all NIH requirements for training in human subjects protection.

C. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI grant program director responsible for the grant

This clinical research trial uses commercial agents and there is no associated Investigational New Drug (IND) or Investigational Device Exemption (IDE). Any temporary or permanent suspension, as determined by the PI, IRB, or DSMC, of this clinical research trial will be reported to the NCI grant program director by the PI.

D. Plans for assuring data accuracy and protocol compliance

Collaborating sites send signed consents, eligibility forms, and CRFs with source documents demonstrating eligibility, treatment, and serious adverse events (if applicable) to the study staff. These are reviewed for eligibility, adherence to the protocol, accuracy, and completeness by the study staff. Queries are sent to the collaborating investigators if CRFs are inaccurate or incomplete.

The study is monitored under the FHCRC Monitoring Plan. The FHCRC Data and Safety Monitoring Plan detail the full scope and extent of monitoring and provides for immediate action in the event of the discovery of major deviations.

14. Records

Clinical Statistics maintains a patient database at FHCRC to allow storage and retrieval of patient 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. Any publication or presentation will refer to patients by this number and not by name. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are kept in a locked room. They are maintained by the FHCRC data collection staff which is supervised by an A.R.T. Access is restricted to personnel authorized by the Division of Clinical Research.

Standard data collection procedures have been developed and agreed upon by the research physicians at FHCRC and all collaborating study centers for previous protocols. Ongoing data collection will be monitored by the coordinating center to ensure data completeness and uniformity across study centers. Follow-up once the patient leaves the research center will be primarily through the patient's physician and through annual clinic visits at the transplant research center.

Collection of Survival and Disease Response Data

Centers enrolling patients will complete case report forms within 120 days of HCT that detail events occurring within the 100 days after HCT (Appendix K). The case report form provides detailed descriptions of the transplantation procedure, disease response, and complications. Detailed treatment-related adverse events will be reported using the NCI Common Toxicity Criteria (Appendix M). The coordinating center will contact subjects when they return to the HCT center for routine HCT follow-up at 3, 6, 12, 18 and 24 months and then annually time five years, to ascertain the patient's disease status and survival. Referring physicians are required to report the date and cause of death within 48 hours of occurrence. Supporting medical records must be available upon request to substantiate data on the case report forms. Death information including date and cause will be reviewed from these medical records, and will be confirmed by death certificate.

15. Statistical Considerations and Termination of the Study

This phase II trial will enroll 30 patients with high-risk multiple myeloma, lymphoma, or CLL. Patients will receive an autologous HCT, followed by nonmyeloablative conditioning and allogeneic HCT from a HLA-haploidentical related donor. We anticipate average annual accrual of 4 patients per year from SCCA with an average duration of 12 years to complete the study.

In case of a cross-over from this protocol to another tandem autologous-allogeneic research protocol (#1409 or other appropriate protocol) or vice versa, enrollment will be counted on the crossed-over protocol if the patient receives the allogeneic transplantation on that protocol. If the patient is crossed-over but does not receive the allogeneic transplantation, enrollment will be counted on the initial protocol.

The primary objective of this study is to examine the potential efficacy of this treatment plan in terms of **progression free survival (PFS)**. PFS will be calculated for all patients from the date of autologous transplant until the time of death. Nonmyeloablative conditioning and HCT from HLA- haploidentical related donors resulted in 1-year PFS of 32% among patients with high-risk hematological malignancies. Our hypothesis is that the addition of planned autologous HCT will improve PFS by reducing the rates of relapse. Given the relatively poor prognostic characteristics of patients eligible for this study, an observed 1-year PFS of ≥50% would be considered efficacious and worthy of further study. With 30 patients, the width of an 80% binomial confidence interval for the PFS probability would be +/- 10 percentage points; the width of the 95% confidence interval would be +/- 18 percentage points. With 30 patients, the probability of observing 1-year PFS of 0.50 or greater is 57% if the true rate is 0.50, 77% if the true rate is 0.55, and 90% if the true rate is 0.60.

The secondary objectives of this study are to assess rates of relapse at 1 year, early NRM and incidence/severity of acute and chronic GVHD, and immune reconstitution after allografting.

Reconstitution of lymphocyte subsets in peripheral blood at is a secondary endpoint. Absolute counts of B-cells ($CD19^+$), T-cell subsets (determined by differential expression of CD4, CD8 or CD45 isoforms on $CD3^+$ cells) and NK cells ($CD16^+/CD56^+$) in peripheral blood determined on day +84 should be compared to pre-transplant lymphocyte counts on day –6.

NRM after nonmyeloablative HLA-haploidentical HCT was 15% at 1-year. Therefore, we will choose a NRM at 200 days after allograft of 30% as a threshold for a safety stopping rule. This allows for some increase in NRM due to additional patients being exposed to the risk of NRM if we are successful in reducing the rate of relapse/progression. It also allows for a small amount of NRM after the autograft. Early NRM will be monitored in a sequential fashion. A stopping rule will be implemented for:

- NRM within 200 days of the allograft exceeds 30%.

Reasonable evidence will be taken to mean that the lower bound of a one-sided 80% confidence interval for the true rate of NRM is above 0.30. Operationally, these limits would be realized if any of the failure rates below are observed:

- NRM within 200 days of allograft (30% threshold): 5/10, 9/20, 12/30

These stopping rules will be evaluated at least every 10 patients. Patients may continue to be enrolled pending evaluation of the safety endpoints in each cohort of 10 patients; however, the outcome of subsequent patients cannot be used to override a stopping rule triggered in the earlier cohort. The operating characteristics of these stopping rules are summarized in the table below.

Table 12: Operating Characteristics of Stopping Rules

True rate of day 200 NRM	Probability of early stopping*	Average n at stopping*
0.35	45%	24
0.40	66%	21
0.45	81%	19

* based on 10,000 Monte Carlo simulations

Since there is limited experience treating patients with lymphoma, Waldenstrom's Macroglobulinemia, CLL, MM, or plasma cell leukemia with the treatment plan proposed in the current study, this trial will be carefully monitored for potential complications that could render this proposal a failure relative to more conventional treatment plans for eligible patients. In addition to the above outcomes, secondary endpoints to be examined include overall survival, relapse rate, and engraftment. Overall survival will be estimated by the method of Kaplan and Meier, and relapse rate will be summarized using cumulative incidence estimates. Confidence intervals for all these outcomes will be also be estimated. Engraftment will be monitored in a sequential fashion. Given the preliminary experience with nonablative HCT in patients with lymphoma, Waldenstrom's Macroglobulinemia, CLL, MM, or plasma cell leukemia, we do not expect engraftment failure or rejection to be a problem in this population undergoing reduced-intensity allografting, but we will be concerned should the observed rejection- or engraftment-failure rate exceed 20%. Should this occur, the study would be suspended pending review by the DSMB.

As stated above, should the results of this study indicate that the current treatment plan is potentially efficacious, a more definitive analysis of efficacy will be undertaken in a subsequent Phase II study. This future study would be designed to show a statistically significant difference in PFS compared to a predetermined fixed target rate.

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APPENDICES

Table of Contents

APPENDIX A
THE KARNOFSKY PERFORMANCE STATUS SCALE

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

APPENDIX B
THE LANSKY PLAY-PERFORMANCE SCALE
(FOR USE WITH PERSONS AGES 1 – 16 YEARS)

Score (%)	Description
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both, greater restrictions of, and less time spend in play activities
60	Up and around, but minimal active play, keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play; able to participate in all quiet play activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	Unresponsive
0	Dead

Appendix C
INFECTIOUS DISEASE GUIDELINES

Please note that the content of these PDFs is from the Fred Hutchinson Clinical Research Division Standard Practice Manual and does not contain research related procedures.

Herpes Simplex and Varicella Zoster Virus Prevention and Treatment

hsv-vzv.pdf

CMV Prevention: Surveillance and Preemptive Therapy

cmvprevention.pdf

CMV Disease: Diagnosis and Treatment

cmvdiseasetreatmen
t.pdf

Antifungal Therapy Guidelines

antifungal_therapy.p
df

Pneumonia / Pneumocystis Jiroveci Prophylaxis

pneumocystisjiroveci
.pdf

Antibiotic Prophylaxis for Encapsulated Bacteria in Allogeneic Patients with Chronic GvHD Requiring Immunosuppressive Therapy

antibioticprophylaxisf
orencapsulatedbacte

Vaccinations

Vaccines

Foscarnet

foscarnet.pdf

APPENDIX D
GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE

Severity of Individual Organ Involvement		
Skin	+1	a maculopapular eruption involving less than 25% of the body surface
	+2	a maculopapular eruption involving 25-50% of the body surface
	+3	generalized erythroderma
	+4	generalized erythroderma with bullous formation and often with desquamation
Liver	+1	bilirubin (2.0-3.0 mg/100 ml)
	+2	bilirubin (3-5.9 mg/100 ml)
	+3	bilirubin (6-14.9 mg/100 ml)
	+4	bilirubin > 15 mg/100 ml
Gut	Diarrhea is graded +1 to +4 in severity. Nausea and vomiting and/or anorexia caused by GVHD is assigned as +1 in severity The severity of gut involvement is assigned to the most severe involvement noted. Patients with visible bloody diarrhea are at least stage +2 gut and grade +3 overall	
Diarrhea	+1	≤ 1000 ml of liquid stool/day* (≤ 15ml of stool/kg/day)†
	+2	>1,000 ml of stool/day* (> 15ml of stool/kg/day)†
	+3	>1,500 ml of stool/day* (> 20ml of stool/kg/day)†
	+4	2,000 ml of stool/day* (≥ 25ml of stool/kg/day)†

**In the absence of infectious/medical cause*
†For pediatric patients

Severity of GVHD	
Grade I	+1 to +2 skin rash
	No gut or liver involvement
Grade II	+1 to +3 skin rash
	+1 gastrointestinal involvement and/or +1 liver involvement
Grade III	+2 to +4 gastrointestinal involvement and/or
	+2 to +4 liver involvement with or without a rash
Grade IV	Pattern and severity of GVHD similar to grade 3 with extreme constitutional symptoms or death

a From "Graft-vs-host disease" Sullivan, Keith M. *Hematopoietic Cell Transplantation* Ed: D. Thomas, K. Blume, S. Forman, Blackwell Sciences; 1999, pages 518-519

APPENDIX E
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. In addition, a morbidity scale has been developed to help grade the severity of manifestation of chronic GVHD (Appendix D) at the time of diagnosis, when changes in treatment are made and when assessing treatment response.

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	**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 FEV_1 <80% of predicted with either an FEF 25-75 <65% of predicted or RV >120% of predicted, or a decrease of FEV_1/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 HSCT

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 (see Appendix C).

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 F

Evaluation of Disease Response:

A. Multiple Myeloma, Waldenstrom's macroglobulinemia, or plasma cell leukemia:

Complete remission:

1. Complete disappearance of serum M protein and urine globulins.
2. Absence of new bone lesions.
3. Normal bone marrow aspirate and biopsy as defined by less than 5% plasma cells and normal histology.
4. Normal peripheral blood counts.
5. Normal serum calcium level.
6. Absence of disease at any other previously involved site (e.g., CNS, extramedullary plasmacytomas, etc.).

Partial remission:

1. Greater than 75% reduction in serum M protein.
2. Greater than 90% decrease in 24 hour urine globulin excretion.
3. Size and number of lytic bone lesions must not increase.

Patients who do not meet these criteria are considered to be non-responders.

B. Lymphomas or Waldenstrom's Macroglobulinemia:

Complete remission:

Normalization for ≥ 1 month of all pretransplant markers of disease as assessed by CT scans and by morphologic and flow cytometric examination of bone marrow and peripheral blood.

Complete disappearance of serum M protein and urine globulins (for Waldenstrom's Macroglobulinemia)

Partial remission:

Fifty percent or greater reduction in all markers of disease as assessed by CT scans and by morphologic and flow cytometric examination of bone marrow and peripheral blood, sustained for ≥ 1 month**.**

Greater than 75% reduction in serum M protein (for Waldenstrom's Macroglobulinemia)

Patients who do not meet the criteria for complete or partial remission are considered to be non-responders.

C. CLL

Modified response criteria based on the NCI-Working Group and the International Workshop Group Joint Formal Criteria for evaluating disease response for CLL. [1-3]

Complete Remission (CR)	
Imaging studies (Xray, CT, MRI) (nodes, liver, and spleen)	Normal
Peripheral blood by flow cytometry	No clonal lymphocytes
Bone marrow by flow cytometry	No clonal lymphocytes
Bone marrow by morphology	No nodules; or if present, nodules are free from CLL cells by immunohistochemistry
Duration	≥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 (PR):	
Both criteria:	
Absolute lymphocyte count in peripheral blood	≥50% decrease[3]
Physical exam/Imaging studies (nodes, liver, and/or spleen)	≥50% decrease[3,4]
Duration	≥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
Lymph node Biopsy	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.	

[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.

1. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, Rai KR. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 87: 4990-4997, 1996.

2. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, Hillmen P, Keating MJ, Montserrat E, Rai KR, Kipps TJ, International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines [Erratum appears in Blood. 2008 Dec 15;112(13):5259]. Blood 111: 5446-5456, 2008.

3. Chronic lymphocytic leukemia: recommendations for diagnosis, staging, and response criteria. International Workshop on Chronic Lymphocytic Leukemia. Ann Intern Med 110: 236-238, 1989.

APPENDIX G

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 regardless of the policies of the institution. 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 must 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 unexpected and **serious adverse events which may be due to study treatment or intervention** must **be reported to the FHCRC Institutional Review Office as soon as possible but within at least 10 calendar days of the investigator learning of the event.**

Definitions

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.

Life-threatening Adverse Event – Any adverse event that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction. Study toxicities are graded using the NCI Common Toxicity Criteria (where appropriate use the criteria for transplant patients.) All Grade 4 (life-threatening) toxicities in Appendix M occurring between start of conditioning and day 200 that meet expedited reporting requirements must be reported as soon as possible but within at least 10 calendar days of the investigator learning of the event.

Unexpected Adverse Event – An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). If applicable product information is not available, such as for studies that do not involve pharmaceutical products or devices, an unexpected adverse event is an adverse event that was not described in the study protocol or informed consent.

Serious Adverse Event (SAE) – Any adverse event occurring that results in any of the following outcomes:

- Death – start of conditioning to day 200, regardless of cause,
- a life-threatening adverse event (see above)
- a persistent or significant disability/incapacity,
- a congenital anomaly
- requires intervention to prevent permanent impairment or damage.

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 nonmyeloablative 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.

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.

Attribution - The FHCRC designation for the determination of whether an adverse event is related to a medical product, treatment or procedure will be as follows:

- Related – includes adverse events that are definitely, probably, or possibly related to the medical treatment or procedure.
- Not Related – includes adverse events are doubtfully related or clearly not related to the medical treatment or procedure.

The FHCRC Serious Adverse Event (SAE) Report Form should be completed for all adverse events that meet the expedited reporting requirements. All available information should be submitted but it is acceptable to fax an incomplete report form at the initial report. A completed report should be faxed as soon as possible but must be received within 10 calendar days.

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.

Serious adverse events that do not meet the requirement for expedited reporting (not related to study treatment or expected) will be reported to the IRB as part of the annual renewal of the protocol.

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.

Procedure for Reporting Serious and Unexpected Adverse Events from Participating Sites

Regulations defining the responsibilities for reporting serious and unexpected adverse reactions are defined above. Serious and unexpected adverse events must be reported to the FHCRC Investigator within 10 days of learning of the event. This includes patient deaths, regardless of cause (serious, unexpected, and related/possibly related), occurring start of conditioning - day 200 post-transplant procedure. The immediate telephone report must be followed by faxed comments to the Trial Coordinator at **(206) 667-5378.** This will be followed by detailed written report (See Appendix "H") 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.

Obligation of Investigators

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 Case Report Form (**Appendix K)**. 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 modified (for HSCT) NCI Common Toxicity Criteria (**Appendix M**). Attributes will include a description, date of onset, maximum severity, and assessment of relationship to the study agent or other suspect agent(s).

Adverse events will be graded accordingly: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening or debilitating, and 5 = fatal. All Grade 4 (life-threatening) or Grade 5 (fatal) events on the Adapted HSCT NCI scale meet expedited reporting requirements.

Association or relatedness to the study agent will be graded as follows: 1 = unrelated, 2 = unlikely, 3 = possibly, 4 = probably, and 5 = definitely related.

V. Case Report Forms

Case report forms must be completed for all patients registered onto the protocols and submitted to the FHCRC data coordinating center. The first case report form (day 28) is due on day 50. For outside centers a Staging Form must accompany the form with the patient staging at registration, day 28, day 56, day 84 and day 100. Staging forms should also be completed with each Follow Up Form completed on day 180, 1 year, 1.5 years, 2 years, 3 years, and yearly thereafter. For Outside Centers, case report forms are expected to be submitted no later than 30 days following the scheduled follow up date. A DLI Form must be completed and submitted for every infusion given.

VI. Protocol Monitoring

As the coordinating center, FHCRC will monitor accrual at the outside institutions. 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 treatment
   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 that was approved by the institution's IRB. IRB approval and reapproval are documented including appropriate use of full-board review and proper review of appropriate amendments or revisions
   3. 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 H

Fred Hutchinson Cancer Research Center

Clinical Research Division

Institutional Review Office

SERIOUS ADVERSE EVENT REPORT (SAE) Form IRO-08

FHCRC IR File Number: _____ FHCRC Protocol Number: _____

FHCRC Unique Patient # _____ ☐ FHCRC/SCCA ☐ Other

Gender: ☐ Male ☐ Female Age: _____

FHCRC Principal Investigator: _____

Phone Number: _____ Mailstop: _____

Date of Report: _____

☐ Initial Report _____ ☐ Follow-Up Report # _____ ☐ Other

Date Serious Adverse Event Started: _____

Date study staff became aware of event: _____

Date Ended: _____ Or ☐ Ongoing (if ongoing – must submit follow up report)

Adverse Event: _____

_____

Describe the Serious Adverse Event including a summary of all relevant clinical information.
(Or attach a MedWatch Form or other SAE reporting form if one has been completed.) Use Page 2, if necessary: _____

_____

Outcomes Attributed to adverse event: (Check all that apply)

☐ Death ____/____/____
☐ Life-Threatening
☐ Hospitalization (initial or prolonged)
☐ Disability
☐ Congenital Anomaly
☐ Required intervention to prevent permanent impairment/damage

Specify Agent(s) and/or Procedure(s) involved in this protocol:

#1 _____ #2 _____

Pharmaceutical product/medical treatment/procedure

☐ Not Related (Unrelated, Unlikely)
☐ Related (Possible, Probable, Definite)

Pharmaceutical product/medical treatment/procedure

☐ Not Related (Unrelated, Unlikely)
☐ Related (Possible, Probable, Definite)

☐ Follow-up Report Required ☐ Final Report (PI must sign final report)

Report Completed by: _____ Date: _____

The PI has determined that the consent form must be revised: ☐ Yes ☐ No

Does this study involve the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA, into human subjects (human gene transfer)? ☐ yes ☐ no If yes and the activity involves the SCCA outpatient clinic, a copy of this Protocol Modification Form and any supporting documents to be reviewed and approved, will be forwarded to the FHCRC's Institutional Biosafety Committee (IBC) by the Protocol Office (Mailstop: LM-230).

_____ _____

Signature of Principal Investigator Date:

Fred Hutchinson Cancer Research Center
Clinical Research Division
Institutional Review Office
SERIOUS ADVERSE EVENT REPORT (SAE) Form IRO-08

FHCRC IR File Number: _____ FHCRC Protocol Number: _____

FHCRC Unique Patient # _____ Date of Report: _____

Describe the Serious Adverse Event including a summary of all relevant clinical information.

APPENDIX I

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 J

Protocol 2241 Patient Demographics and Eligibility Form

Please Fax this completed form to (206)-667-5378 for patient registration

UPN: _____

Research Subject Name: _____ _____ ____
(Last) *(First)* *(MI)*

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

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

Patient Diagnosis: _____

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

Disease Status: _____

Ethnicity *(choose one): Instruct the research subject 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 research subject 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**

Inclusion Criteria

1. ☐ Yes ☐ No Patient signed and dated consent form.
   Date: _____
   Date of IRB approval of consent form: _____
   IRB file: _____

Questions #2-6 must be marked "Yes" Or "NA" for the patient to enroll on 2241.

2. ☐ Yes ☐ N/A **Lymphoma:** Patients with i) diagnosis of NHL or HL, of any histological grade, ii) Refractory or relapsed disease after standard chemotherapy, and iii) High risk of early relapse following autograft alone.

3. ☐ Yes ☐ N/A **Waldenstrom's Macroglobulinemia-** Must have failed 2 courses of therapy

4. ☐ Yes ☐ N/A **CLL:**

i. Patient with

a) Diagnosis of T-cell CLL or T-cell PLL who have failed initial chemotherapy, patients with T cell CLL or PLL **OR**

b) Diagnosis of B-cell CLL, B-cell small lymphocytic lymphoma, or B-cell CLL that progressed to prolymphocytic leukemia (PLL), who either:

I) Failed to meet NCI Working Group criteria[2] (**Appendix F**) for complete or partial response after therapy with a regimen containing fludarabine (or another nucleoside analog, e.g. 2-CDA, pentostatin) or experience disease relapse within 12 months after completing therapy with a regimen containing fludarabine (or another nucleoside analog).

II) Failed any aggressive chemotherapy regimen, such as FCR, at any time point.

III) Have "17p deletion" cytogenetic abnormality and relapsed at any time point after initial chemotherapy.

Describe which inclusion is specific for this patient:_____
_____.

ii. Patient must meet harvesting criteria for autologous HCT:
a) previously collected PBMC may be used
b) circulating cells <5000

iii. Marrow involvement with CLL cells <50%

5. ☐ Yes ☐ N/A **MM**: Patients who

i. Have received induction therapy for a minimum of 4 cycles.

ii. In addition, patients **must meet at least one of the following criteria I-IX** (I-VII: at time of diagnosis or pre-autograft):

I) Any abnormal karyotype by *metaphase* analysis except for isolated t(11,14)
II) FISH translocation 4:14
III) FISH translocation 14:16
IV) FISH deletion 17p
V) β2-microglobulin > 5.5 mg/ml
VI) Cytogenetic hypodiploidy
VII) Plasmablastic morphology (≥2%)
VIII) Recurrent or non-responsive (less than PR) MM after at least two different lines of conventional chemotherapy.
IX) Progressive MM after a previous autograft (provided stored autologous CD34 cells are available)

Describe which inclusion is specific for this patient:_____
_____.

6. ☐ Yes ☐ N/A **Plasma cell leukemia**: after induction chemotherapy

7. ☐ Yes ☐ No Age ≤75 years.

8. ☐ Yes ☐ No Detectable tumor prior to mobilization regimen.

Exclusion Criteria

Each of the following questions must be marked "No" Or "NA" for the patient to enroll on 2241.

1. ☐ Yes ☐ No Life expectancy severely limited by disease other than malignancy.

2. ☐ Yes ☐ No Seropositive for the human immunodeficiency virus

3. ☐ Yes ☐ No ☐ N/A Female who is Pregnant or Breastfeeding

4. ☐ Yes ☐ No ☐ N/A Fertile men or women unwilling to use contraceptive techniques during and for the 12 months following treatment

5. ☐ Yes ☐ No CNS involvement with disease refractory to intrathecal chemotherapy

6. ☐ Yes ☐ No Patients with active non-hematologic 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.

7. ☐ Yes ☐ No Patient with fungal infection and radiological progression after receipt of amphotericin B or active triazole for greater than 1 month

8. ☐ Yes ☐ No Patient with symptomatic coronary artery disease or ejection fraction <40% or other cardiac failure requiring therapy (or, if unable to obtain ejection fraction, shortening fraction of < 26%). Ejection fraction is required if the patient has a history of anthracyclines or history of cardiac disease.
NOTE: If shortening fraction is <26%, a cardiology consult is required. The PI of the study must approve eligibility

PI Signature: _____ Date: _____

9. ☐ Yes ☐ No Corrected DLCO < 50% of predicted, FEV1 <50% of predicted, and/or receiving supplementary continuous oxygen.
NOTE: The FHCRC PI of the study must approve of enrollment of all patients with pulmonary nodules.

PI Signature: _____ Date: _____

10. ☐ Yes ☐ No Liver function abnormalities: Patient with clinical or laboratory evidence of liver disease will be evaluated for the cause of liver disease, its clinical severity in terms of liver function, bridging fibrosis, and the degree of portal hypertension. The patient will be excluded if he/she is found to have fulminant liver failure, cirrhosis of

the liver with evidence of portal hypertension, alcoholic hepatitis, esophageal varices, a history of bleeding esophageal varices, hepatic encephalopathy, uncorrectable hepatic synthetic dysfunction evinced by prolongation of the prothrombin time, ascites related to portal hypertension, bacterial or fungal liver abscess, biliary obstruction, chronic viral hepatitis with total serum bilirubin >3mg/dL, or symptomatic biliary disease.

11. ☐ Yes ☐ No Patient has a Karnofsky score less than 50% Lansky score less than 40%

12. ☐ Yes ☐ No Patients with poorly controlled hypertension despite multiple antihypertensives

*Note – the HCT-Comorbidity score is: _____

Planned donor stem cell source is:

☐ Bone Marrow

☐ PBMC

PI Initials: _____Date:_____

Signature of person completing form: _____ Date:_____

Signature of Principal Investigator:_____ Date:_____

APPENDIX K

Core Case Report Form

Acrobat Document

APPENDIX L

Intrathecal Diagnostics and Therapeutics

Please note that the content of this PDF is from the Fred Hutchinson Clinical Research Division Standard Practice Manual and does not contain research related procedures.

intrathecaltherapy-combined.pdf

Appendix M

Adapted from COMMON TOXICITY CRITERIA (CTC)

ALLERGY/IMMUNOLOGY		
Adverse Event	**Grade 3**	**Grade 4**
Allergic reaction/ hyper-sensitivity (including drug fever)	Symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	Anaphylaxis
Vasculitis	Requiring steroids	Ischemic changes or requiring amputation
Allergy/Immunology – Other (specify):_____	Severe	Life-threatening or disabling
BLOOD/BONE MARROW		
Adverse Event	**Grade 3**	**Grade 4**
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	Requiring transfusion and/or medical intervention (e.g., steroids)	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
For BMT studies, if specified in the protocol. For pediatric BMT studies, if specified in the protocol.	>4 u pRBC in 24 hours >30mL/kg in 24 hours	Hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin Hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
CARDIOVASCULAR - ARRHYTHMIA		
Adverse Event	**Grade 3**	**Grade 4**
Cardiovascular/Arrhythmia - Other (specify): _____ _____	Symptomatic, and requiring treatment of underlying cause	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR - GENERAL		
Adverse Event	**Grade 3**	**Grade 4**
Acute vascular leak syndrome	Respiratory compromise or requiring fluids	Life-threatening; requiring pressor support and/or ventilatory/support
Cardiac-ischemia/infarction	Angina without evidence of infarction	Acute myocardial infarction

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

CARDIOVASCULAR - GENERAL (cont'd)		
Adverse Event	**Grade 3**	**Grade 4**
Cardiac left ventricular function	CHF responsive to treatment	Severe or refractory CHF or requiring intubation
Cardiac troponin I (cTnI)	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	≥ 0.1 - <0.2ng/mL	≥ 0.2ng/mL
Hypotension	Requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	Shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Myocarditis	CHF responsive to treatment	Severe or refractory CHF
Pericardial effusion/ pericarditis	With physiologic consequences	Tamponade (drainage or pericardial window required)
Syncope (fainting) is graded in the Neurology category.	-	-
Thrombosis/embolism	Deep vein thrombosis, requiring anticoagulant therapy	Embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the Cardiovascular (general) category.		
Cardiovascular/General – Other (specify):_____	Severe	Life-threatening or disabling

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

COAGULATION		
Adverse Event	**Grade 3**	**Grade 4**
DIC (disseminated intravascular coagulation) Also consider Platelets. *Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.*	Laboratory findings present with no bleeding	Laboratory findings and bleeding
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTA or hemolytic uremic syndrome/HUS) Also consider Hemoglobin, platelets, creatinine. *Note: Must have micro-angiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).*	Laboratory findings present without clinical consequences Evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	Laboratory findings and clinical consequences, (e.g., CNS hemorrhage/bleeding or thrombosis/embolism or renal failure) requiring therapeutic intervention Evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy.
Coagulation - Other (specify): _____	Severe	Life-threatening or disabling
CONSTITUTIONAL SYMPTOMS		
Adverse Event	**Grade 3**	**Grade 4**
Weight gain associated with Veno-Occlusive Disease (VOD) for BMT studies, if specified in the protocol. Also consider Ascites Edema, Pleural effusion (non-malignant).	>10% or as ascites	>10% or fluid retention resulting in pulmonary failure
DERMATOLOGY/SKIN		
Adverse Event	**Grade 3**	**Grade 4**
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	Life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Rash/desquamation associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	Symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area.	Generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

GASTROINTESTINAL		
Adverse Event	**Grade 3**	**Grade 4**
Ascites (none-malignant)	Symptomatic, requiring therapeutic paracentesis	Life-threatening physiologic consequences
Colitis Also consider Hemorrhage/ bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, melena/GI bleeding, rectal bleeding/hematochezia, hypotension.	Abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	Perforation or requiring surgery or toxic megacolon
Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol. *For pediatric BMT studies, if specified in the protocol.* Also consider Hemorrhage/ bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, pain, dehydration, hypotension.	>1500mL of diarrhea/day *>15mL/kg of diarrhea/day*	Severe abdominal pain with or without ileus
Duodenal ulcer (requires radiographic or endoscopic documentation)	Uncontrolled by outpatient medical management; requiring hospitalization	Perforation or bleeding, requiring emergency surgery

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

GASTROINTESTINAL (cont'd)		
Adverse Event	**Grade 3**	**Grade 4**
Gastric ulcer (requires radiographic or endoscopic documentation) Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.	Bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	Perforation or bleeding, requiring emergency surgery
Gastritis Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.	Uncontrolled by out-patient medical management; requiring hospitalization or surgery	Life-threatening bleeding, requiring emergency surgery
Pancreatitis Also consider Hypotension. *Note: Amylase is graded in the METABOLIC/LABORATORY category.*	Abdominal pain with pancreatic enzyme elevation	Complicated by shock (acute circulatory failure)
Mucositis *Note: Radiation-related mucositis is graded as Mucositis due to radiation.*	Painless erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Typhlitis (inflammation of the cecum) Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, hypotension, febrile neutropenia.	Abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	Perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

HEMORRHAGE		
Notes: *Transfusion in this section refers to pRBC infusion.* *For any bleeding with grade 3 or 4 platelets (<50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider Platelets, Transfusion: pRBCs, and Transfusion: platelets in addition to grading severity by grading the site or type of bleeding.* *If the site or type of Hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: NS Hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/ hematochezia, Vaginal bleeding.*		
Adverse Event	**Grade 3**	**Grade 4**
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia Also consider Platelets, hemoglobin, transfusion: platelets, transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage – Other (specify site):_____ *Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.*	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia Also consider Platelets, hemoglobin, transfusion: platelets, transfusion: pRBCs, hemorrhage – Other (specify site): _____ *Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the Hemorrhage category. Also grade as Other in the Hemorrhage category.*	Requiring transfusion	Catastrophic bleeding requiring major non-elective intervention

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

HEMORRHAGE (cont'd)		
Adverse Event	**Grade 3**	**Grade 4**
CNS hemorrhage/bleeding	Bleeding noted on CT or other scan with no clinical consequences	Hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Hemoptysis	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Melena/GI bleeding	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Rectal bleeding/hematochezia	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
Hemorrhage – Other (specify site): _____	Requiring transfusion	Catastrophic bleeding, requiring major non-elective intervention
HEPATIC		
Adverse Event	**Grade 3**	**Grade 4**
Bilirubin Bilirubin associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	>3.0 – 10.0 x ULN >6 - <15mg/100mL	>10.0 x ULN >15mg/100mL
INFECTION/FEBRILE NEUTROPENIA		
Adverse Event	**Grade 3**	**Grade 4**
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection).	Present	Life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia – Other (specify): _____	Severe	Life-threatening or disabling

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

NEUROLOGY		
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.		
Adverse Event	**Grade 3**	**Grade 4**
CNS cerebrovascular ischemia	Transient ischemic event or attack (TIA)	Permanent event (e.g., cerebral vascular accident)
Leukoencephalopathy associated radiological findings	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)	Severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)
Seizure(s)	Seizure(s) in which consciousness is altered	Seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
PULMONARY		
Adverse Event	**Grade 3**	**Grade 4**
Adult Respiratory Distress Syndrome (ARDS)	-	Present
Apnea	Present	Requiring intubation
Carbon monoxide diffusion capacity (DLCO)	>25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
FEV1	>25 - <50% of pretreatment or normal value	<25% of pretreatment or normal value
Hypoxia	Decreased O2 saturation at rest, requiring supplemental oxygen	Decreased O2 saturation, requiring pressure support (CPAP) or assisted ventilation

Appendix M (cont'd)
Adapted from COMMON TOXICITY CRITERIA (CTC)

RENAL/GENITOURINARY		
Adverse Event	**Grade 3**	**Grade 4**
Creatinine *Note: Adjust to age-appropriate levels for pediatric patients.*	>3.0- 6.0 x ULN	>6.0 x ULN
Renal failure	Requiring dialysis, but reversible	Requiring dialysis and irreversible
SECONDARY MALIGNANCY		
Adverse Event	**Grade 3**	**Grade 4**
Secondary Malignancy – Other (specify type): _____ *Excludes metastasis from initial primary.*	-	Present

Appendix N

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

Assign scores appropriately if the patient has any of these comorbidities

*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.

Appendix O

Weight / Adjusted Body Weight for Drug Dosing


weight_for_drug_do
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APPENDIX P

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 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 Q

Salmon and Durie Criteria for Diagnosis of Multiple Myeloma

1. Major criteria

    i. Plasmacytoma on tissue biopsy.
    ii. Bone marrow plasmacytosis with > 30% plasma cells.
    iii. Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for IgG peaks or 2.0 g for IgA peaks, > 1.0 g/24 h of k or l light chain excretion on urine electrophoresis in the absence of amyloidosis.

2. Minor criteria

    a. Bone marrow plasmacytosis with 10% to 30% plasma cells.
    b. Monoclonal globulin spike present, but less than the levels defined above.
    c. Lytic bone lesions.
    d. Normal IgM <50 mg, IgA <100 mg, or IgG <600 mg/dL.

Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b.

1. i + b, i + c, i + d (i + a not sufficient)
2. ii + b, ii+ c, ii + d.
3. iii + a, iii + c, iii + d.
4. a + b + c, a + b + d.

APPENDIX R

Radiotherapy Treatment Guidelines


TBI_Pediatric_NON_Myeloablative.pdf


TBI_Adult_Non_Myeloablative.pdf