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TITLE: ***A PHASE II STUDY OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT FOR B–CELL NON–HODGKIN LYMPHOMA USING ZEVALIN®, FLUDARABINE AND MELPHALAN***

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NOTE: This protocol was written in compliance with the policies and procedures of *THE CITY OF HOPE NATIONAL MEDICAL CENTER HEMATOPOIETIC CELL TRANSPLANT PROGRAM; CLINICAL MANUAL; STANDARD OPERATING POLICIES AND PROCEDURES; SEPTEMBER 2004.* Sections in this protocol followed by Ω § [#] refer to information found in the *HCT CLINICAL MANUAL.*

1.0 PROPOSED STUDY

As a member of the West Coast Transplant Consortium (WCTC), City of Hope National Medical Center (COHNMC) has extensive experience with the use of Reduced Intensity Conditioning (RIC) regimens. Fludarabine, 125 mg/m^2 and Melphalan, 140 mg/m^2 followed by Allogeneic Hematopoietic Stem Cell Transplant (AHSCT) has been used effectively with limited toxicity in patients with hematologic malignancies.[1, 30] However, relapse remains a significant cause of failure for patients with aggressive histologies.[31]

Because of its relative safety and ability to target radiation directly to lymphoma cells, IDEC–2B8–MX–DTPA [Ibritumomab Tiuxetan (Zevalin®)] will be combined with the RIC regimen of Fludarabine and Melphalan. This preparative regimen will be used in selected patients with relapsed or refractory Low–Grade Lymphoma (LGL), Mantle Cell Lymphoma (MCL) and Intermediate–Grade Non–Hodgkin Lymphoma (IG NHL). The goal of this protocol is to use Zevalin® to increase the anti–lymphoma effect in these B–Cell lymphomas while at the same time preserving the adoptive immunotherapeutic Graft–Versus–Lymphoma (GVL) effect and low Transplant–Related Mortality (TRM) associated with our current RIC regimen.

This study will be a Phase II trial of 46 patients focusing on TRM, Relapse–Free Survival (RFS), Overall Survival (OS) and toxicity. Early stopping rules will be incorporated for safety outcomes. However, there will be no early stopping based on efficacy. For details on stages of accrual and sample size requirements, please refer to *§ 14.0 STATISTICAL CONSIDERATIONS*.

2.0 OBJECTIVES

2.1 To evaluate the safety and efficacy of a preparative regimen of Yttrium–90 (^{90}Y)–Labeled Anti–CD20 Monoclonal Antibody (MAb) in combination with Fludarabine and Melphalan followed by Allogeneic Hematopoietic Stem Cell Transplant (APBSCT) for treatment of patients with B–Cell Low–Grade Non–Hodgkin Lymphoma (LG NHL), Intermediate–Grade Non–Hodgkin Lymphoma (IG NHL) and Mantle Cell Lymphoma (MCL).

2.2 To evaluate the short– and long–term complications of this new preparative regimen, including rates of engraftment, Acute and Chronic Graft–Versus–Host–Disease (GVHD) and infectious complications.

2.3 To estimate the disease response rate, disease relapse (progression) rate, and non-relapse mortality rate.

2.4 To perform exploratory studies that seek to measure/characterize the expression of costimulatory molecules and impact of these molecules on the NK and T cells of a subset of lymphoma patients pre- post- ASCT and the stem cell product from a portion of sibling donors.

3.0 BACKGROUND AND RATIONALE

3.1. INTRODUCTION

Non–Hodgkin Lymphoma (NHL) is the fifth most common cancer in the United States. According to the American Cancer Society (ACS), approximately 58,870 people in the United States will be diagnosed with Hodgkin Disease (HD) or NHL, and an estimated 18,840 will die from either disease in 2006. These numbers include both adults and children. But the incidence of most types of indolent and aggressive lymphomas increases with age. It is estimated that a person's risk of developing the disease in his or her lifetime is approximately 1 in 50. The risk of dying of the disease is about 1 in 100. This cancer is somewhat more common in men than in women. Men have a 1 in 46 risk of developing NHL over his lifetime. Women have a 1 in 55 risk of developing NHL over her lifetime. Whites are affected more often than African Americans or Asian Americans. Between 1973 and 1996 the incidence of NHL increased by 80% in the United States.[2]

Based on unique clinicopathologic features defined in the Revised European American Classification of Lymphoid Malignancies (REAL) and World Health Organization (WHO) classification system, Diffuse Large–Cell Lymphoma (DLCL), Follicular Lymphoma (FL) and MCL are diagnosed in approximately 31%, 22%, and 6%, respectively, of all new adult lymphoma diagnoses.[3] Approximately 30–40% of patients with DLCL can be cured with conventional chemotherapy,[4] whereas MCL and LGL are incurable with similar therapies.[5]

High–Dose Therapy (HDT) with autologous Hematopoietic Stem Cell Transplantation (aHSCT) can rescue patients with DLCL who fail to achieve a remission or relapse after initial therapy, but treatment failure occurs in the majority of these patients, with Long–Term Survival (LTS) seen in approximately 30–40% of these patients.[6, 7] Relapse is also common after aHSCT for MCL and FL.[8]

Relapse after aHSCT may be the result of tumor contamination of the re–infused Stem Cells (SCs) or intrinsic resistance of malignant cells to HDT. Moreover, many patients fail to collect adequate numbers of SCs due to Bone Marrow (BM) involvement with lymphoma or extensive prior chemoradiotherapy. Patients who relapse after conventional therapy and cannot undergo aHSCT, or those relapsing after this procedure usually have short median survivals.

Allogeneic donors can provide an alternative source of healthy Hematopoietic Stem Cells (HSCs) for these patients, with the added benefit of a potential GVL effect. The GVL effect in lymphoma has been demonstrated by the efficacy of Donor Lymphocyte Infusions (DLIs) after relapse from all AHSCTs [9, 10, 11] and by the observation that relapses occur less frequently after AHSCT as compared to aHSCT.[12, 13, 14] This effect is more pronounced in the LGLs. The evidence for a GVL effect in MCL and DLCL is weaker, coming from studies reporting responses following withdrawal of immunosuppression or coincidental with the development of GVHD[15], decreased relapse rates in patients with GVHD,[16, 17] remissions after DLI and relapses in patients with graft rejection.[18, 19] The potential benefit of the GVL effect from AHSCT has been offset in most cases by the increased toxicity of this procedure compared to aHSCT, resulting from Regimen–Related Toxicity (RRT) and GVHD. To try to improve these results, RIC regimens have been successfully developed, allowing adequate engraftment in most cases and decreasing the RRT considerably. These regimens rely predominantly on the GVL effect for their success. As expected, patients with malignancies that are more vulnerable to this effect, such as LGLs and Chronic Lymphocytic Leukemia (CLL), have benefited more from this approach.[20] Conversely, decreasing the power of the regimen may compromise disease control for patients with High(er)–Grade Lymphomas (HGLs) and other aggressive hematological malignancies. This issue cannot be overstated given the observation that relapse contributes significantly to treatment failure and that chemosensitivity consistently appears predictive of outcome following AHSCTs for NHL and Acute Myelogenous Leukemia (AML).[9, 21, 22, 30]

The study will also focus on costimulatory receptors, namely, PD-1, CTLA-4, CD28, ICOS, OX40 and 4-1BB (CD137), and will be performed on blood samples collected at various time points before and after the AHSCT regimen, using either FACS analysis or mRNA Q-PCR. The results may contribute to a better understanding of immune factors important in outcome. To date, we have shown that the PD-1 molecule was up-regulated in HCT subjects before the development of CMV disease. Similar techniques will be used for the expression of the other costimulatory receptors.

Therefore, improving the potency of the conditioning regimen for lymphoma with targeted therapies, such as radioimmunoconjugates, would be a desirable goal in the AHSCT setting, by combining improved tumor control with a potential GVL effect, without significantly increasing RRT.

3.2 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (AHSCT) FOR NON–HODGKIN LYMPHOMA (NHL)

The use of AHSCT in the treatment of NHL is increasing. Although there are no large prospective randomized trials comparing the outcome of aHSCT versus AHSCT in NHL, most retrospective comparisons suggest that there is a lower risk of relapse following AHSCT, particularly in patients with LGL. Unfortunately, AHSCT is also associated with a higher rate of early and late TRM, which tends to offset any potential advantage conferred by the reduced risk of relapse.

We recently evaluated the long–term results in 55 patients who underwent a traditional myeloablative AHSCT at COHNMC between 1/91 and 5/99.[23] All patients have had adequate follow–up to determine LTS and risk of relapse. In this study the median age was 40.7 years (range 18–54). Fifteen patients (27%) had LGL, 16 patients (29%) had Intermediate–Grade Lymphoma (IGL), 8 patients (15%) had MCL and 16 patients (29%) had HGL. In this series, 93% of patients had advanced disease including relapse, PR after initial treatment or Progressive Disease (PD) during induction or multiple relapses. The majority of patients received a Fractionated Total Body Irradiation (FTBI) containing regimen. At the time of this analysis, 29 patients (53%) were alive. Overall, the TRM was 29% and the relapse rate was 20%. The Kaplan–Meier estimates for the 2 year OS and RFS rates for the entire group were 46% and 42% *(see FIGURE 1A* and *FIGURE 1B)*. The 2 year OS probability by histologic subtypes were: LGL 83%, IGL 33%, HGL 0%, and MCL 56%, with a statistically significant difference seen between LGL and HGL patients based on the log–rank test (p=0.0110) *(see FIGURE 2)*.

FIGURE 1A

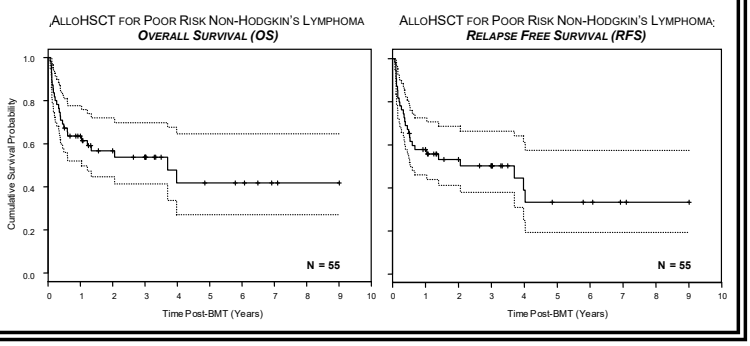
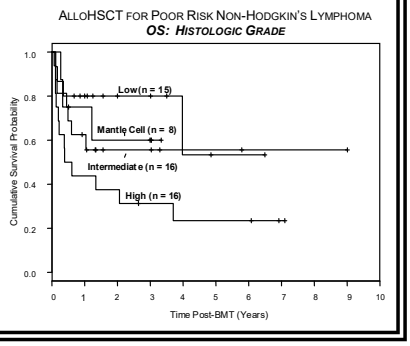


FIGURE 1B

FIGURE 2



These results suggest that AHSCT is an effective therapeutic strategy in selected patients with poor risk or refractory lymphoma. Compared to aHSCT, the relatively lower risk of relapse observed in this study is in agreement with other reported trials, which suggest that AHSCT introduces a GVL effect.[24, 25, 26] Although the median age of patients with LGL and MCL is about 60 years, the median age of patients in our study was 40–41 years because, as commonly is the case, older patients were excluded because of concerns over the higher TRM and mortality associated with conventional Total Body Irradiation (TBI) based allografting in older patients. Thus, the use of non–myeloablative or RIC regimens and AHSCT as part of a clinical trial should be explored for an older, less robust patient population and for those patients who would not be candidates to receive an aHSCT.

Recent studies conducted in the WCTC involving primarily the Fred Hutchinson Cancer Center (FHCC), COHNMC and Stanford University have explored the use of a potentially less toxic approach to allografting for older patients (≥ 50 years) with LG NHL, AML and multiple myeloma – diseases not readily cured by autografting.[27, 28] These studies are based on the use of potent immunosuppression using Fludarabine, low dose TBI, Cyclosporine A (CSA) and Mycophenolate Mofetil (MMF) to limit the risk of graft rejection and GVHD and thereby establish mixed chimerism as identified in a preclinical canine model. Updates of these trials have evaluated the efficacy of establishing mixed or full donor hematopoietic chimerism using a non–myeloablative and relatively non–toxic conditioning regimen for allogeneic engraftment and to obtain preliminary data on GVL or Graft–Versus–Tumor (GVT) effects in a variety of tumor types and clinical situations (remissions, relapse). The results from treatment of lymphoma with this approach for 74 patients (29 DLCL, 16 MCL and 29 LGL) show a Progression–Free Survival (PFS) of 48% at 1 year for the whole group. When analyzed by histology, the more aggressive form of the disease showed a PFS of 35% with a relapse rate of 33% while those patients with LGL showed a RFS of 60% and relapse of 16% with a median follow–up of a little > 1 year.[29]

Based on the idea that some component of anti–tumor activity, in addition to the anti–tumor allogeneic response would be necessary for patients with this disease to improve the overall outcome, without increasing the toxicity, at COHNMC we conducted a parallel study to those active in the consortium with a regimen of Fludarabine and Melphalan (140 mg/m^2). In this Phase I/II Trial of 40 patients, all patients received Human Leukocyte Antigen (HLA) matched related or unrelated

transplant and all engrafted with full chimerism. Disease–Free Survival (DFS) was 54% at 1 year for all patients, 67% for LGL and 48% for DLCL. Similar to the more RIC approach of our studies with Seattle, relapse was more common in those patients with advanced DLCL.[30]

In summary, taken together, the 2 studies, along with data from MD Anderson Cancer Center [20, 21, 31] suggest that the RIC AHSCT approach is very effective in some patients with lymphoma. The therapy appears to be more successful in controlling disease for those patients with LGL and that relapse is higher in patients with more aggressive histology, despite the apparent GVL effect that is a major component of the treatment. Thus, based on the clinical and toxicity observations we have to date concerning the incorporation of the radiolabeled anti CD20 antibody into the aHSCT regimen,[32] [33] we hypothesize that we can augment the anti–tumor efficacy of the allogeneic RIC regimen by the addition of antigen specific RIT against the CD20 antigen on B–Cell lymphoma, without an increase in RRT for patients with advanced lymphoma who would not be good candidates to benefit from the autologous approach (BM/blood involvement, multiple relapsed LGL, MCL).

3.3 MANTLE CELL LYMPHOMA (MCL)

3.3.1 AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT (aHSCT) FOR MANTLE CELL LYMPHOMA (MCL)

MCL is associated with a poor prognosis and median OS of 3 years when treated with standard chemotherapy. Advanced stage disease, including BM and Peripheral Blood (PB) involvement, is commonly seen at diagnosis. Response to conventional treatment approaches such as CHOP chemotherapy tends to be poor and PD is usually seen within 12–18 months.[1]

A recent update of the combined COHNMC/Stanford experience with 45 MCL patients undergoing aHSCT showed a higher OS and Event–Free Survival (EFS) rate for patients undergoing transplantation in *first remission* (CR1) (n=16) compared to patients beyond CR1 (n=29).[34] In this analysis, the median follow–up was 2.6 months. The OS and EFS were 94% and 87% for CR1 patients compared to 61% and 38%, respectively, for patients beyond CR1. Relapse rate was lower (8% vs 56%) in CR1 patients.

Other studies have yielded conflicting results from aHSCT for MCL. Some show inferior outcome compared with historical controls,[35] and continued trend of relapse,[8, 36] whereas others suggest apparent benefit.[37, 38] Other studies support our observation that aHSCT may be more effective in CR1.[39-42]

In summary, results from these studies have not clarified the role of aHSCT in the treatment of MCL due to lack of controlled studies; patients in CR1 appear to benefit most. The routine use of this procedure cannot be routinely recommended outside of clinical protocols.

3.3.2 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (AHSCT) FOR MANTLE CELL LYMPHOMA (MCL): CONVENTIONAL MYELOABLATIVE REGIMENS

The literature is limited for allogeneic HSCT for MCL. Few studies have examined conventional dose conditioning regimens for this histology; in heavily pre–treated patients, EFS and OS at 2–3 years were around 50%–60%, in registry and single institution studies.[18, 43] This is in agreement with our experience with conventional myeloablative regimens in 10 patients with MCL with a 5 year probability of OS and PFS of 40–50%.[23, 30]

3.3.3 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (AHSCT) FOR MANTLE CELL LYMPHOMA (MCL): REDUCED INTENSITY CONDITIONING (RIC) REGIMENS

An appealing strategy for MCL is the use of RIC regimens, given that most patients are older and experience excessive toxicity from conventional myeloablative regimens. Conflicting results have been reported in this setting.

At COHNMC, 5 patients with relapsed MCL underwent sibling AHSCT utilizing Fludarabine and Melphalan as conditioning regimen, with CSA and MMF as GVHD prophylaxis. Patients were heavily pre–treated with a median of 3 prior regimens. Three patients had failed aHSCT. Three patients had chemosensitive disease at the time of transplantation. All patients engrafted. At a median follow up of 13 months, 2 patients are alive without evidence of PD; 2 patients have relapsed and died of PD and 1 died of acute GVHD without evidence of disease.[30]

The WCTC has transplanted 16 patients with MCL using a non–myeloablative regimen of Fludarabine and single dose TBI, with CSA and MMF as GVHD prophylaxis. Nine patients are alive in remission at 8–36 months after HSCT.[29]

A single institution study of 18 patients with advanced/relapsed MCL conditioned with Fludarabine, Cyclophosphamide (Cy) and Rituxan® or Cisplatin, Fludarabine and Cytarabine followed by matched sibling or unrelated HSCT, with Tacrolimus and Methotrexate for GVHD prophylaxis, was performed at MD Anderson.[21] Patients were heavily pre–treated with a median of 3 prior regimens. Four patients had relapsed after aHSCT. All patients engrafted and none experienced > grade 2 acute GVHD. Seventeen patients achieved a CR. Three patients relapsed post–transplant. One of these patients achieved a CR after DLI. At a median 26 month follow up, the current EFS was 82%.

In contrast to MD Anderson and WCTC studies, a retrospective analysis from the European Bone Marrow Transplantation (EBMT) Lymphoma Registry reported poor outcomes in this setting.[9] Twenty–two heavily pre–treated patients with advanced MCL, 36% of who had failed previous aHSCT, were conditioned with a Fludarabine based regimen in 84% and BEAM in 10% of patients. Sixteen patients had chemosensitive disease at the time of transplant. The 2 year PFS, OS and TRM were of 0%, 13%, and 82%, respectively. The TRM in this series is higher than most studies with RIC regimens.

Overall, the experience with AHSCT for MCL is limited. Relapse remains a significant cause of treatment failure, and may be more common after RIC regimens than with conventional myeloablative regimens. This issue, coupled with the anecdotal evidence of a GVL effect in MCL, the exquisite radiosensitivity of MCL and the generally older age of these patients, provides the rationale for enhancing the efficacy of RIC regimens with radioimmunoconjugates prior to AHSCT.

3.4 Diffuse Large–Cell B–Cell Non–Hodgkin Lymphoma (B–DLCL NHL)

3.4.1 autologous Hematopoietic Stem Cell Transplant (aHSCT) for Diffuse Large–Cell B–Cell Non–Hodgkin Lymphoma (B–DLCL NHL)

The role of aHSCT for DLCL in chemosensitive relapse has been well established in a randomized study, with 46% of patients in the transplant arm enjoying durable remissions compared to 12% of patients salvaged with chemotherapy alone.[6] Many patients considered for this approach, however, remain refractory to salvage therapy or may not collect adequate SCs due to tumor contamination or insufficient BM reserve from prior therapy.

Convincing data has also emerged for the role of aHSCT in high risk DLCL patients in CR1, though this is not widely accepted. More controversy exists regarding the role of this procedure for patients with chemorefractory disease, with few patients achieving long–term remissions.[44]

3.4.2 Allogeneic Hematopoietic Stem Cell Transplant (AHSCT) for Diffuse Large–Cell Lymphoma (DLCL): Conventional Myeloablative Regimens

A multicenter study from France reported 5 year OS and DFS of 41% and 40% in 73 patients with aggressive lymphomas, excluding Burkitt's and lymphoblastic lymphoma.[45] Similarly, a registry analysis from the EBMT including 147 patients with IG NHL found a 4 year PFS and OS of 35% and 38%, respectively; in this study, Chronic GVHD was associated with a lower risk of relapse.[13] Our results in 16 patients with IGL in this setting showed an actuarial 2 year OS and PFS of 50%, with a low relapse rate of 10%. [23, 30]

3.4.3 Allogeneic Hematopoietic Stem Cell Transplant (AHSCT) for Diffuse Large–Cell Lymphoma (DLCL): Reduced Intensity Conditioning (RIC) Regimens

Low numbers of patients with DLCL treated with RIC regimens have been reported, with PFS rates of 20–55%. A registry analysis from the EBMT showed high rates of relapse for a heterogeneous group of HG NHL, including several with DLCL, with 1 year PFS of 32%.

Similarly, our experience at COHNMC with Fludarabine and Melphalan in 12 patients with B–DLCL undergoing sibling (7) or unrelated donor (5) transplantation shows a low 2 year OS and PFS of 36% and 17% with a high relapse rate of 76%.[30]

The WCTC transplanted 18 patients with DLCL with the non–myeloablative regimen of Fludarabine and TBI. Eight patients are alive in remission, 4 have died of PD, 2 are alive in relapse, and 4 have died of non–relapse causes.[29]

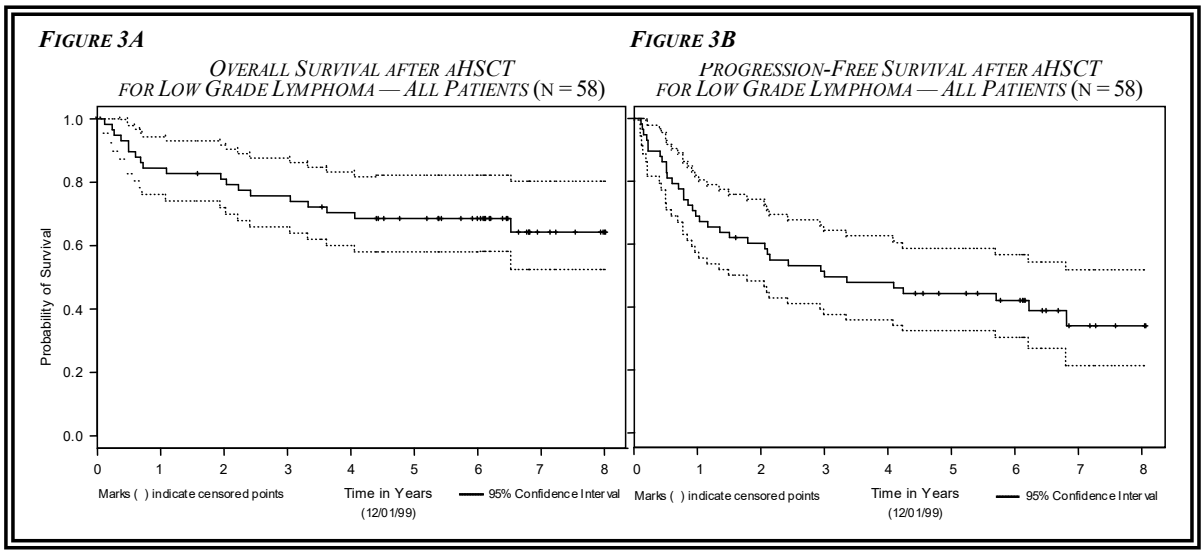
These results with AHSCT for DLCL suggest a higher relapse rate with RIC than with conventional regimens, and would provide the rationale for augmenting the preparative regimen with targeted therapies.

3.5 Low–Grade Non–Hodgkin Lymphoma (LG NHL)

3.5.1 *autologous Hematopoietic Stem Cell Transplant (aHSCT) for Low–Grade Lymphoma (LGL)*

Current treatment approaches are generally not curative in patients with advanced stage LG NHL although many in this patient population have indolent clinical courses. Standard treatments often produce high Response Rates (RRs), but CR1 duration ranges from 12–36 months.[46-48] Relapsed LGL often responds to salvage therapy. However, duration of subsequent remissions progressively decreases.

HDT and aHSCT have been shown to improve PFS and increase the duration of remission in select patients with chemosensitive relapsed LG NHL.[49-54] We have analyzed engraftment, toxicity, treatment outcome and prognostic factors in 58 patients with a history of LG FL who underwent HDT and aHSCT from 1991–1995 at COHNMC.[53] Although prolonged OS *(see Figure 3A)* and PFS can be seen after aHSCT *(see Figure 3B)*, long–term follow–up demonstrates a continuous risk of relapse. Interventions aimed at decreasing the risk of relapse (ie, Rituximab for post–transplant consolidation and/or *in vivo* purging) are being investigated in this setting.



Studies from COHNMC[53] and Stanford[54] suggest that the use of a FTBI containing preparative regimen is associated with a higher OS and PFS rate, perhaps reflecting the exquisite sensitivity of LGLs to radiation therapy. This observation supports the exploration of using intensified target doses of radiation such as radiolabeled antibodies in the conditioning regimen to maximize the anti–lymphoma effect of the transplant. However, because of the long natural history and continued pattern of relapse after aHSCT *(see FIGURE 3B)*, the curative potential of autografting in patients with relapsed LGL has not been established. Moreover, an increased risk of Myelodysplasia Syndrome (MDS) is observed in this patient population, indicating a need for close monitoring and reporting long–term follow–up of studies in this area.[55]

New treatment modalities, including the use of MAbs, radioimmunoconjugates, lymphoma vaccines and antisense molecules, have been introduced into the treatment armamentarium for the various types of NHLs. Some of these agents are being incorporated into aHSCT and AHSCT strategies, as discussed below.

3.5.2 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (AHSCT) FOR LOW–GRADE NON–HODGKIN LYMPHOMA (LG NHL)

Outcomes for LGLs after AHSCT are generally better than for more aggressive NHL, with PFS and EFS rates of 50%–80% and low relapse rates of 10–20%,[56, 57] suggesting an important role for GVL in curing these malignancies. As such, RIC regimens are particularly appealing in this setting. A recent report from MD Anderson showed a 2 year DFS of 84%, with a TRM of 5% and no relapses in 18 patients with chemosensitive FL (n=18), and CLL/Small Lymphocytic Lymphoma (SLL) (n=2), conditioned Fludarabine, Cy, with or without Rituximab.[20] The EBMT reported a 2 year PFS, PD and TRM of 54%, 21% and 31%, respectively, in 52 patients with LG NHL receiving a RIC regimen.[9]

Similarly, the outcome for 34 patients with B–Cell LG NHL transplanted at COHNMC with conventional dose regimens (n=18) and a RIC regimen of Fludarabine and Melphalan (n=16) was similar in terms of relapse rates (15% versus 17%), with 2 year OS/PFS rates of 56%/50% and 74%/61%, (p–values of 0.45 and 0.78), suggesting that RIC regimens provide similar disease control to conventional dose regimens, with less TRM.

3.6 RADIOIMMUNOTHERAPY (RIT) FOR B–CELL NON–HODGKIN LYMPHOMA (NHL)

Recently, Radioimmunotherapy (RIT) has emerged as a promising treatment for NHL. Radioisotope labeled MAbs provide a mechanism for targeting radiation preferentially to tumor sites, while sparing normal tissues. B–Cell lymphomas are an attractive target for RIT because of their radiosensitivity, their well defined surface antigens, and the availability of multiple MAbs to those antigens.

Iodine–131 (^{131}I) has been the gold standard for RIT due to its long track record in treating thyroid cancer, its well–defined radiochemistry, its clinical availability, and its potential for both Radioimmunoimaging (RII) and RIT. However, there are disadvantages of ^{131}I, including its long 8–day half life, the risks of radiation exposure to health care providers and the non–specific irradiation to normal organs from the gamma (γ) components of ^{131}I.

Recent RIT trials for lymphoma have utilized ^{131}I labeled anti–B1 (anti–CD20) antibody, with results suggesting that ^{131}I labeled anti–B1 is safe and effective and may induce prolonged CR in heavily pre–treated LG and transformed LG NHL.[58-60] Although additional studies are needed, ^{131}I anti–B1 antibody can be safely given in combination with HD chemotherapy in an aHSCT setting for NHL.[60]

Yttrium–90 (^{90}Y) may be an ideal radionuclide for RIT since it emits beta (β) particles that are more potent than those delivered by ^{131}I. It is a pure β emitter, making it a safer reagent for medical personnel to administer than ^{131}I. In addition, the short half–life also facilitates the use of ^{90}Y in combination with other agents, (ie, chemotherapy) and allows for high dose rates at localized sites. Unfortunately, ^{90}Y cannot be used for RII due to its absence of γ emissions. Indium–111 (^{111}In) has been substituted as an imaging reagent to show tumor localization in patients scheduled for ^{90}Y therapy, on the assumption that its biodistribution closely mimics that of ^{90}Y.

3.6.1 SINGLE–AGENT ZEVALIN® FOR RELAPSED LOW–GRADE NON–HODGKIN LYMPHOMA (LG NHL)

The efficacy of the Zevalin® regimen was evaluated in 2 multicenter studies[61, 62] enrolling a total of 197 subjects:

STUDY 1 was a single arm study of 54 patients with relapsed FL refractory to Rituxan® treatment. Patients were considered refractory if their last prior treatment with Rituxan® did not result in a CR or Partial Response (PR), or if Time–to–[Disease] Progression (TTP) was < 6 months.[61] The primary efficacy endpoint of the study was the Overall Response Rate (ORR). Secondary efficacy endpoints included TTP and Duration of Response (DR). In a secondary analysis comparing objective response to the Zevalin® regimen with that observed with the most recent treatment with Rituxan®, the median DR following the Zevalin® regimen was 6 months vs 4 months. *TABLE 1* summarizes efficacy data from this study and STUDY 2.

STUDY 2 was a randomized, controlled, multicenter study comparing the Zevalin® regimen to treatment with Rituxan®.[62] The trial was conducted in 143 patients with relapsed or refractory LG or follicular NHL, or transformed B–Cell NHL. A total of 73 patients received the Zevalin® regimen, and 70 patients received Rituxan® given as an intravenous (iv) infusion at 375 mg/m^2 weekly x 4 doses. The primary efficacy endpoint of the study was to determine the ORR. The ORR was significantly higher (80% vs 56%, p=0.002) for patients treated with the Zevalin® regimen. The secondary endpoints, DR and TTP, were not significantly different between the 2 treatment groups on this study.

TABLE 1: SUMMARY OF CLINICAL EFFICACY DATA†

	STUDY 1	STUDY 2	
	ZEVALIN® THERAPEUTIC REGIMEN n=54	ZEVALIN® THERAPEUTIC REGIMEN n=73	RITUXAN® n=70
ORR£ (%)	74	80	56
CRRΦ (%)	15	30	16
CRu Rateπ (%)	0	4	4
Median DRƒ,$ (Months) [Range*]	64 [0.5 – 24.9+]	13.9 [1.0 – 30.1+]	11.8 [1.2 – 24.5]
Median TTPƒ,¢ (Months) [Range*]	6.8 [1.1 – 25.9+]	11.2 [0.8 – 31.5+]	10.1 [0.7 – 26.1]

† Efficacy Data Based on International Workshop Response Criteria (IWRC).
£ Overall Response Rate
Φ Complete Response Rate
π Complete Response Rate Unconfirmed
ƒ Estimated with Observed Range
$ Duration of Response: Interval from Onset of Response to Progression of Disease (PD)
* + Indicates an Ongoing Response
¢ Time to Progression: Interval from First Infusion to Progression of Disease (PD)

Adverse Events (AEs) observed in previous trials of the Zevalin® regimen were primarily hematologic, transient, and reversible. Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 32%, 8.5%, and 4.3% of patients, respectively. Hematologic levels recovered in all patients, except when patients went on to other therapy or had pre–existing cytopenias. The severity of hematologic toxicity was related to baseline platelet count and percent BM involvement.

The most frequent, non–hematologic AEs (asthenia, chills, fever, nausea, and headache) were related to accompanying Rituxan® infusions. No major acute organ dysfunction was seen. B–Cell depletion recovered 6–9 months after therapy. Median serum immunoglobulins remained within the normal range and were relatively stable throughout the treatment period and follow–up. The formation of Human Anti–Murine Antibodies (HAMA) or Human Anti–Chimeric Antibodies (HACA) occurred after the Zevalin® regimen in < 2% of patients. T–cells were not depleted. The incidence of severe infection was low (7.6% of patients hospitalized during the treatment period). No observable age–dependent differences were seen in the safety profile. Rare cases of MDS observed were within the expected rate for this heavily pretreated patient population.

3.6.2 SINGLE–AGENT ZEVALIN® FOR MANTLE CELL LYMPHOMA (MCL)

Experience with Zevalin® as single agent for MCL is limited. Younes reported 9 heavily pre–treated patients, 6 of whom were chemorefractory to their previous regimen. The ORR was 33%, with 2 CRs and 1 PR, with the most common toxicity being hematological.[63]

3.6.3 ZEVALIN® AS PART OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT (aHSCT)

Use of high–dose RIT with Zevalin® plus high–dose chemotherapy followed by aHSCT is being investigated at COHNMC and other centers for the treatment of poor risk NHL.[32, 33, 64] Preliminary observations indicate that Zevalin® can be combined with high–dose chemotherapy followed by aHSCT.

Investigators in Seattle have assessed biodistribution toxicities and efficacy of ^{131}I anti–CD20 antibody in patients with B–Cell lymphoma undergoing aHSCT. Patients were assessed with a test dose and those study subjects determined to have tumor doses > liver, lungs and kidney, were eligible for therapeutic infusion of ^{131}I labeled antibody in this Phase I/II transplant trial. Of 43 patients, 24 achieved favorable biodistributions and 19 subsequently received therapeutic infusions of approximately 232–777 mCi of ^{131}I labeled antibody at a dose of 58–1168 mg. This was followed by autologous BM re–infusion.

Sixteen patients achieved a CR, 2 patients PR and 1 a minor response. In their series 9 patients remain in continuous CR (PFS) between 3–53 months. This study indicates a 95% RR in patients able to demonstrate favorable biodistribution, with manageable toxicity, particularly with provision for autologous BM support.

Further studies from this group sought to determine the MTD of ^{131}I anti–CD20 antibody that could be combined with Etoposide (VP–16) and Cy. Fifty–two patients with relapsed lymphoma were studied who received a therapeutic dose of 1.3 mg/kg protein labeled with iodine calculated to deliver a targeted dose of radiation (20–27 Gy) to critical organs. In this, the DFS after 2 years was 68%. Investigators in Nebraska have also combined ^{131}I anti–CD20 antibody to a regimen of high–dose chemotherapy (BEAM) with encouraging results in patients with relapsed lymphoma.

An analysis of these studies suggest that the burden of tumor, the dose of antibody administered, the presence of circulating antigen, and the rate of antigen modulation may influence the biodistribution of radiolabeled antibodies and the efficacy of RIT. Similar to problems with immunotoxin therapy, larger tumor masses present formidable penetration barriers to antibodies because of the inefficiency of diffusion that exists in bulkier disease. This latter problem may be addressed by using alternative radionuclides whose particle energy (MeV) and path length may be more favorable for treating bulky disease. It is for this and the results we have obtained in this program and other reasons summarized below that we have focused on the use of ^{90}Y labeled antibodies in the treatment of patients with B–Cell lymphoma who are candidates for aHSCT.

Patients with B–Cell lymphoma (LGL, MCL, DLCL) expressing the CD20 antigen on the cell surface are the target for this approach with particular emphasis on developing regimens that can be used to cure lymphoma in older patients where the disease is more common and transplant based therapeutics are limited. Our studies indicate that the disease is sensitive to radiolabeled therapy and in the high–dose setting some patients can achieve long–term control of the disease. For patients with advanced lymphoma, we utilized a dosimetry–based high–dose ^{90}Y anti–CD20 immunoconjugate combined with high–dose VP–16 60 mg/kg and Cy (100 mg/kg), the 2 year DFS was 81% with a relapse rate 15% without an increase in transplant toxicity or compromise of engraftment. For those older patients with lymphoma, a ^{90}Y anti–CD20 antibody was added at a high–dose regimen of BEAM. With a median age of 61 (40–81) 17 patients have received treatment. Currently, 70% of the patients are alive and PFS is with a median follow–up of 12 months. We had hypothesized that a major contributing cause of relapse following autologous Bone Marrow Transplant (aBMT) is the residual sites of disease, and that ^{90}Y labeled CD20 specific MAb may be utilized to increase the targeted efficacy of the preparatory regimen used for patients undergoing transplantation for B–Cell lymphoma. The short half life of this heavy metal also leads to an increased dose rate at tumor sites, which can enhance the therapeutic killing effect. Of additional importance, the high emission (2.3 MeV max) allows for more effective crossfire from targeted cells to cells that have not been bound by antibody, either for antigenic reasons or for tumor bulk. The average path length is 6 mm in contrast to iodine which is 0.8 mm (59). Localization of any released ^{90}Y to bone will also increase the BM dose, which is an important residual site in patients with lymphoma, particularly those with follicular histology.

The results described above for incorporation of radiolabeled anti–CD20 antibody therapy for younger and older patients with lymphoma undergoing aHSCT, and the data obtained for the patient trial of RIC AHSCT, provide the rationale for a clinical trial to incorporate an effective targeted anti–tumor agent as a component of the RIC AHSCT regimen for patients with lymphoma who are not candidates for aHSCT.

3.6.4 RADIATION DOSIMETRY

Estimations of Radiation Absorbed Doses (RADs) for ^{111}In–Zevalin® and ^{90}Y–Zevalin® were performed using sequential Whole (Total) Body Images (WBIs) and *MIRDOSE 3* software.[20, 41] Estimated RADs to organs and BM from a course of the Zevalin® therapeutic regimen are summarized in *TABLE 2*. Absorbed dose estimates for lower large intestine, upper large intestine, and small intestine have been modified from the standard *MIRDOSE 3* output to account for the assumption that activity is within the intestine wall rather that the intestine contents.

TABLE 2 ESTIMATED RADIATION ABSORBED DOSES (RADS) TO ORGANS AND MARROW FROM A COURSE OF THE ZEVALIN® THERAPEUTIC REGIMEN

ORGAN	^{90}Y–ZEVALIN® MGY/MBQ		^{111}IN–ZEVALIN® MGY/MBQ	
	MEDIAN	RANGE	MEDIAN	RANGE
Spleen[1]	9.4	1.8 – 14.4	0.9	0.2 – 1.2
Testes[1]	9.1	5.4 – 11.4	0.6	0.4 – 0.8
Liver[1]	4.8	2.3 – 8.1	0.7	0.3 – 1.1
Lower Large Intestinal Wall[1]	4.8	3.1 – 8.2	0.4	0.2 – 0.6
Upper Large Intestinal Wall[1]	3.6	2.0 – 6.7	0.3	0.2 – 0.6
Heart Wall[1]	2.8	1.5 – 3.2	0.4	0.2 – 0.5
Lungs[1]	2.0	1.2 – 3.4	0.2	0.1 – 0.4
Small Intestine[1]	1.4	0.8 – 2.1	0.2	0.1 – 0.3
Red Marrow[2]	1.3	0.7 – 1.8	0.2	0.1 – 0.2
Urinary Bladder Wall[3]	0.9	0.7 – 2.1	0.2	0.1 – 0.2
Bone Surfaces[2]	0.9	0.5 – 1.2	0.2	0.1 – 0.2
Ovaries[3]	0.4	0.3 – 0.5	0.2	0.2 – 0.2
Uterus[3]	0.4	0.3 – 0.5	0.2	0.1 – 0.2
Adrenals[3]	0.3	0.0 – 0.5	0.2	0.1 – 0.3
Brain[3]	0.3	0.0 – 0.5	0.1	0.0 – 0.1
Breasts[3]	0.3	0.0 – 0.5	0.1	0.1 – 0.3
Gallbladder Wall[3]	0.3	0.0 – 0.5	0.3	0.1 – 0.4
Muscle[3]	0.3	0.0 – 0.5	0.1	0.0 – 0.1
Pancreas[3]	0.3	0.0 – 0.5	0.2	0.1 – 0.2
Skin[3]	0.3	0.0 – 0.5	0.1	0.0 – 0.1
Stomach[3]	0.3	0.0 – 0.5	0.1	0.1 – 0.2
Thymus[3]	0.3	0.0 – 0.5	0.1	0.1 – 0.2
Throid[3]	0.3	0.0 – 0.5	0.1	0.0 – 0.1
Kidneys[1]	0.1	0.0 – 0.2	0.2	0.1 – 0.2
Total Body[3]	0.5	0.2 – 0.7	0.1	0.1 – 0.2

1 Organ Region of Interest (ROI)
2 Sacrum Region of Interest (ROI)[42]
3 Whole Body Regions of Interest (ROI)

3.7 PERIPHERAL BLOOD B CELL DEPLETION WITH RITUXIMAB

To maximize the therapeutic effects and minimize the side effects of Zevalin, we aim to deplete circulating B-lymphocytes by rituximab prior to the administration of In-111 Zevalin and Y-90 Zevalin. The goal would be to deplete circulating B-lymphocytes but not to saturate the binding sites within the lymphoma cells (lymph nodes). To achieve this goal, a careful and individualized dosing of rituximab would be necessary. From the phase I study of rituximab (65), there was a dose-dependent, rapid, and specific B cell depletion in all patients. It is generally agreed that when there is a detectable level of rituximab in serum, circulating B cell numbers are minimal.

Pharmacokinetic (PK) data obtained from the patients treated in the pivotal rituximab trial have been analyzed by Bernstein et al. (66). At 3 months post-treatment, they found the median serum level in 62 responders was 25.4 μg/ml compared with 5.9 μg/ml in 42 non-responders (p=0.001). In addition, serum levels correlated inversely with bulk of disease. While it is unknown whether the non-responders had less than saturating levels of rituximab within the tumor, it would be reasonable to assume that the serum rituximab level of 25 μg/ml may be too high for the current study.

In this study, we consider a rituximab level at 10 μg/ml would be a reasonable target in achieving sufficient B cell depletion without saturating the CD20 binding sites in the malignant lymph nodes. Since we expect some of the study patients may have a preexisting rituximab from prior therapy, we will test the

rituximab levels in all study patients. Pre-treatment with rituximab may be given on days -21 and -14 according to its serum level.

The level of Rituxan in the serum is measured in a competitive binding assay using a TRF (time resolved fluorometry) format. An anti-mouse IgG Fab antibody is coated on the plate and then standards, control samples are added in addition to dilutions of the patient's serum. A Europium labeled Rituxan is then added. The Rituxan in the serum competes with the Eu-Rituxan-DTPA and the amount of competition is compared to the standard curve. The assay has been validated and is performed under SOPs. This assay is performed by a California licensed Med Tech who has demonstrated his proficiency in performing the assay. The laboratory is run under the continuing supervision of the Department of Pathology. The laboratory is operating under CLIA rules and has been inspected by CAP.

4.0 DRUG FORMULATION Ω §§ A.012, B.002, B.003, E.002–E.003, E.006, G.001–G.002

4.1 RITUXAN® (IDEC–C2B8 OR RITUXIMAB) Ω §§ A.012

4.1.1 *MODE OF ACTION:* genetically engineered chimeric murine/human MAb directed against CD20 antigen on surface of normal and malignant B lymphocytes; an IgG_1 Ig containing murine V_L and V_H chain region sequences and human constant region sequences; composed of 2 V_H chains of 451 aa and 2 V_L chains of 213 aa (based on cDNA analysis) with molecular weight of ~145 kD; has binding affinity for CD20 antigen of ~8.0 nM.

The Fab domain of Rituxan® binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B–Cell lysis *in vitro*. Possible mechanisms of cell lysis include Complement–Dependent Cytotoxicity (CDC) and Antibody–Dependent Cell Mediated Cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL–4 Human B–Cell Lymphoma Line.

Normal Tissue Cross–Reactivity: Rituxan® binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non–lymphoid tissues examined.

4.1.2 *TOXICOLOGY:* infusional toxicity of chills and rigors are common with first administration of Rituxan® but rarely with subsequent doses; decreased rate of infusion and administration of antihistamines can control these toxicities.

4.1.3 *PACKAGING AND FORMULATION:* 10 ml (100 mg) and/or 50 ml (500 mg) pharmaceutical grade glass vials at concentration of 10 mg protein/ml.

4.1.4 *STORAGE AND STABILITY:* vials stable at 2–8°C (36–46°F); NOT to be used beyond expiration date on carton; vials should be protected from direct sunlight; solutions for infusion shown to be stable for additional 24 hours at room temperature; due to absence of preservatives, solutions should be stored refrigerated (2–8°C); no incompatibilities between Rituxan® and polyvinylchloride or polyethylene bags observed.

4.1.5 *ADMINISTRATION:* administered by slow IV infusion having been diluted to 1–4 mg/ml in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. This initial Rituxan® infusion will be through a dedicated line. If patient has had Rituxan before, begin infusion at 100 mg/hr. If no adverse reactions occur, escalate rate gradually at 100 mg/hr every 30 minutes to a maximum of 400 mg/hr. If patient has not had Rituxan before, begin infusion at 50 mg/hr. If no adverse reactions occur, escalate rate at 50 mg/hr every 30 minutes to a maximum of 400 mg/hr. If hypersensitivity or infusion related events develop, the infusion will be temporarily

slowed or interrupted. The infusion can be continued at half the previous rate when symptoms abate.

4.1.6 *SUPPLIER:* commercially available *(Rituxan® will not be provided by Biogen Idec).*

4.1.7 *Refer to RITUXAN® (IDEC–C2B8 OR RITUXIMAB) package insert for more information.*

4.2 ZEVALIN® (IDEC–2B8–MX–DTPA OR IBRITUMOMAB TIUXETAN) Ω §§ A.012

4.2.1 *MODE OF ACTION:* immunoconjugate resulting from thiourea covalent bond between MAb Ibritumomab and linker–chelator Tiuxetan [N–{2–bis(carboxymethyl)amino}–3–(p–isothiocyanatophenyl)propyl]–[N–{2–bis(carboxymethyl)amino}–2–(methyl)–ethyl] glycine; linker–chelator provides high affinity, conformationally restricted chelation site for ^{111}In or ^{90}Y; molecular weight is ~148 kD; antibody moiety is Ibritumomab, murine IgG_1 κ MAb directed against CD20 antigen found on surface of normal and malignant B lymphocytes; produced in Chinese hamster ovary cells and composed of 2 murine λ 1 V_H chains of 445 aa each and 2 κ V_L chains of 213 aa each.

4.2.2 *TOXICOLOGY:* myelosuppression is dose limiting toxicity in standard dosing regimens; with marrow support, liver, kidney, and lung are likely to be dose limiting organs; infusional toxicity of chills and rigors are common with first administration but rarely with subsequent doses; decreasing rate of infusion and administration of antihistamines should control these toxicities. May cause nausea and rarely may cause vomiting.

4.2.3 *PACKAGING AND FORMULATION:* 2 ml glass septum vial containing 2 ml (3.2 mg) in low metal normal saline at 1.6 mg/ml.

4.2.3.1 *^{111}IN–CHLORIDE*: fixed dose 5 mCi of *^{111}In–chloride* supplied in .05 M HCl.

4.2.3.2 *^{90}Y–CHLORIDE:* maximum dose 32 mCi *^{90}Y–chloride* supplied in .05 M HCl.

4.2.4 *STORAGE AND STABILITY:* antibodies stored in investigational pharmacy at 4°C until day of use; once diluted, unlabeled antibody is to be used in ≤ 24 hours if held at 4°C and an additional 12 hours if held at room temperature; radiolabeled solutions should be used in ≤ 6 hours and should be held at 2–8°C until administered.

4.2.5 *ADMINISTRATION:*

4.2.5.1 *IMAGING DOSE:* administered over approximately 10 minutes by slow IV injection following infusion of Rituxan®; 0.22 micron filter must be on line between patient and infusion port; flush line with at least 10 mls of normal saline following ^{111}In–Zevalin® infusion.

4.2.5.2 *THERAPY DOSE*: 0.4 mCi/kg ^{90}Y administered over approximately 10 minutes by slow IV injection following infusion of Rituxan®; 0.22 micron filter must be on line between patient and infusion port; flush line with at least 10 mls of normal saline following ^{90}Y–Zevalin® infusion.

4.2.6 *SUPPLIER:* commercially available *(Zevalin® will not be provided by Biogen Idec).*

4.2.7 *Refer to ZEVALIN® (IDEC–2B8–MX–DTPA OR IBRITUMOMAB TIUXETAN) package insert for more information.*

4.3 FLUDARA® (2–FLUORO–ARA–AMP, FLUDARABINE PHOSPHATE OR FLUDARABINE) Ω §§ E.002–E.003, E.006

4.3.1 *MODE OF ACTION:* Fludarabine Phosphate analogous to that of ara–C and ara–A; active metabolite appears to be triphosphate, F–ara–ATP; like ara–CTP and ara–ATP 2–F–

ara–ATP is substrate for DNA polymerase and is incorporated into DNA causing strand breaks and inhibition of DNA synthesis.

4.3.2 *TOXICOLOGY:* major toxicity has been myelosuppression; at higher dose levels or in patients with renal impairment CNS toxicity seen characterized by numbness, paraparesis and cortical blindness.

4.3.3 *PACKAGING AND FORMULATION:* supplied as white lyophilized solid cake; each vial contains 50 mg Fludarabine Phosphate, 50 mg mannitol and sodium hydroxide to adjust pH to 7.7; when reconstituted with 2 ml sterile water each ml will contain 25 mg of Fludarabine Phosphate.

4.3.4 *STORAGE AND STABILITY:* intact vials are refrigerated (2–8°C); reconstituted solutions should be used in ≤ 8 hours due to lack of preservatives.

4.3.5 *ADMINISTRATION:* dilute dose in D5W or NS and infuse in ≥ 30 minutes iv.

4.3.6 *SUPPLIER:* commercially available.

4.3.7 *Refer to FLUDARA® (2–FLUORO–ARA–AMP, FLUDARABINE PHOSPHATE OR FLUDARABINE) package insert for more information.*

4.4 ALKERAN® (L–PHENYLALANINE MUSTARD, L–PAM or MELPHALAN) Ω §§ E.002–E.003, E.006

4.4.1 *MODE OF ACTION:* alkylating agent.

4.4.2 *TOXICOLOGY:* most commonly reported toxicity is myelosuppression; other commonly reported adverse reactions reported are nausea, vomiting and hypersensitivity reactions.

*4.4.*3 *PACKAGING AND FORMULATION:* supplied as freeze dried powder; each single–use vial contains Melphalan Hydrochloride equivalent to 50 mg Melphalan and 20 mg Providone; each vial of diluent provided contains sodium citrate 0.2 g, propylene glycol 6 ml, ethanol (96%) 0.52 ml and water for injection for total 10 ml; reconstitute each 50 mg vial by rapidly injecting 10 ml diluent provided; immediately shake vial vigorously until clear solution is obtained; provides 5 mg/ml solution.

4.4.4 *STORAGE AND STABILITY:* intact vials stored at room temperature (15–30°C) and protected from light; once reconstituted with diluent provided, solution is chemically stable at room temperature for ≤ 90 minutes.

4.4.5 *ADMINISTRATION:* reconstituted, undiluted Melphalan has been administered *via* CVC line using dose of 100–200 mg/m^2 over 2–20 minutes.

4.4.6 *SUPPLIER:* commercially available.

4.4.7 *Refer to ALKERAN® (L–PHENYLALANINE MUSTARD, L–PAM or MELPHALAN) package insert for more information.*

4.5 PROGRAF® (FK–506 OR TACROLIMUS) Ω §§ G.001–G.002

4.5.1 *MODE OF ACTION:* calcineurin inhibitor; immunosuppressive agent that interferes with IL–2–mediated T–cell activation.

4.5.2 *TOXICOLOGY:* most commonly reported toxicities are renal insufficiency, tremors, hypomagnesaemia, hypertension, hyperglycemia and seizures.

4.5.3 *PACKAGING AND FORMULATION:* supplied as sterile solution in 1 ml ampoules containing equivalent of 5 mg anhydrous Tacrolimus per ml, in boxes of 10 ampoules; also available as 1 mg and 0.5 mg capsules for oral administration.

4.5.4 *STORAGE AND STABILITY:* store at 5–25°C (41–77°F); Prograf® capsules are stored at controlled room temperature, 15–30°C (59–86°F).

4.5.5 *ADMINISTRATION:* injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to concentration of 0.004–0.02 mg/ml; solution should be stored in glass or polyethylene containers and should be discarded if > 24 hours; solution should not be stored in PVC container due to decreased stability and potential for extraction of phthalates; when more dilute solutions are used (eg, pediatric dosing, etc), PVC–free tubing should be used to minimize potential for significant drug adsorption onto tubing; parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit; due to chemical instability of Tacrolimus in alkaline media, Prograf® injection should not be mixed or co–infused with solutions of ≥ pH 9 (eg, ganciclovir or acyclovir).

4.5.6 *SUPPLIER:* commercially available.

4.5.7 *Refer to PROGRAF® (FK–506 OR TACROLIMUS) package insert for more information.*

4.6 RAPAMUNE® (SIROLIMUS) Ω §§ G.001–G.002

4.6.1 *MODE OF ACTION:* induces T–cell apoptosis and unresponsiveness through inhibition of mTOR, a kinase that regulates cell cycle entry in response to IL–2 signaling and other cellular functions.

4.6.2 *TOXICOLOGY:* most commonly reported toxicities are hyperlipidemia, arthralgia, cytopenias, epistaxis, edema and rash.

4.6.3 *PACKAGING, FORMULATION, PREPARATION AND STORAGE:*

4.6.3.1 *SIROLIMUS ORAL SOLUTION:* Rapamune® oral solution (bottles and foil pouches) should be refrigerated at 2–8°C (36–46°F) and protected from light; Rapamune® oral solution is stable for ≤ 24 months under this storage condition; when bottle is opened, it should be kept in refrigerator and contents used in ≤ 1 month; however, both opened bottles and pouches may be stored at room temperature (15–30°C; 59–86°F) for ≤ 1 month; amber syringe and cap provided for dosing from bottle and product may be kept in syringe for ≤ 24 hours at room temperatures ≤ 25°C (77°F) or refrigerated at 2–8°C (36–46°F); syringe should be discarded after single use; after dilution, preparation should be used immediately; Rapamune® oral solution provided in bottles may develop slight haze when refrigerated; if haze occurs, allow product to stand at room temperature and shake gently until haze disappears; presence of haze does not affect quality of product.

4.6.3.2 *SIROLIMUS TABLETS:* Rapamune® tablets are available as white triangular shaped tablets marked *RAPAMUNE 1 mg* in bottles of 100 tablets or as cartons containing 10 blister cards of 10 tablets each; Rapamune® tablets should be stored at 20–25°C (68–77°F); cartons should be used to protect blister cards and strips from light; Rapamune® tablets should be dispensed in a tight, light–resistant container.

4.6.4 *ADMINISTRATION:* for adults, Sirolimus will be administered at 12 mg orally loading dose on DAY –3, followed by 4 mg orally single morning daily dose (target serum level 3–12 ng/ml by HPLC). For Pediatric patients < 40 kg, Sirolimus will be administered at 3 mg/m^2 orally on DAY –3, followed by 1 mg/m^2 orally single morning daily dose. Dosing

of Sirolimus will be based on adjusted ideal body weight. If actual body weight is < ideal body weight, actual body weight will be used.

4.6.5 *SUPPLIER:* commercially available.

4.6.6 *Refer to RAPAMUNE® (SIROLIMUS) package insert for more information.*

4.7 METHOTREXATE

4.7.1 *MODE OF ACTION:* See package insert.

4.7.2 *TOXICOLOGY:* See package insert.

4.7.3 *PACKAGING, FORMULATION, PREPARATION AND STORAGE:* See package insert.

4.7.4 *ADMINISTRATION:* See package insert and COH SOP G.001.04: *Acute Graft versus Host Disease Prophylaxis* http://www.coh.org/hct-sop/Section%20G/G.001.04_Acute_Graft_versus_Host_Prophylaxis.pdf and http://www.coh.org/hct-sop/Section%20G/G.001.04_Acute_Graft_versus_Host_Addendum_A.pdf (accessibility verified 04/01/10)

4.7.5 *SUPPLIER:* commercially available.

4.7.6 *Refer to METHOTREXATE package insert for more information.*

4.8 NEUPOGEN® (G–CSF, GRANULOCYTE–COLONY STIMULATING FACTOR OR FILGRASTIM) Ω §§ B.002, B.003

4.8.1 *MODE OF ACTION:* Filgrastim, recombinant human G–CSF, r–metHuG–CSF, protein produced by *Escheria coli* into which has been inserted human G–CSF, differs from natural protein in that N–terminal amino acid is a methionine and is not glycosylated.

4.8.2 *TOXICOLOGY:* bone pain is major toxicity in Phase II and III trials (20–25% patients); bone pain, often preceded by rise in circulating neutrophil count; occurred more frequently in patients treated with 20–100 µg/kg/day iv and less often in lower and/or subcutaneous doses; pain is generally mild to moderate in severity, usually controlled with non–narcotic analgesics such as acetaminophen; other toxicities include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase and uric acid levels presumed secondary rapid expansion of myeloid compartment; less frequently reported toxicities include subclinical splenomegaly, exacerbation of pre–existing skin rashes, effusions, thrombocytopenia and cutaneous vasculitis.

Rarely, allergic–type reactions occur; since commercial introduction, reports suggest allergic–type reaction (< 1 in 4,000 patients), but immune component has not been demonstrated; these have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin, respiratory and cardiovascular; some reactions occurred in initial exposure; reactions tended to occur in ≤ first 30 minutes after administration and appeared to occur more frequently in patients who received recombinant G–CSF intravenously; rapid resolution of symptoms occurred in most cases after standard supportive care; symptoms recurred in > half patients when rechallenged; recombinant G–CSF should be used with caution in patients with pre–existing cardiac conditions such as hypertension, angina pectoris and cardiac dysrhythmias.

4.8.3 *PACKAGING AND FORMULATION:* supplied as clear, colorless preservative free liquid for parenteral administration; single use vials contain recombinant G–CSF, 300 µg/ml in preservative free solution with 0.59 mg/ml acetate, 50 mg/ml sorbitol, 0.004% Tween 7 80, 0.035 mg/ml sodium, and water for injection, USP, pH 4.0 to make 1 ml; may be diluted in 5% dextrose.

4.8.4 *STORAGE AND STABILITY:* refrigerate at 2–8°C (36–46°F); avoid shaking; may be allowed to reach room temperature for ≤ 24 hours; vials left at room temperature for > 24 hours should be discarded; parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration observed, container should not be used.

Diluted to concentrations of 5–15 Fg/ml should be protected from absorption to plastic materials by adding albumin (human) to final concentration of 2 mg/ml when diluted in 5% dextrose or 5% dextrose plus albumin (human); compatible with glass bottles, PVC and polyolefin iv bags, and polypropylene syringes; dilution to final concentration of < 5 µg/ml is not recommended at any time; do not dilute with saline at any time; product may precipitate.

4.8.5 *ADMINISTRATION:* donors will receive G–CSF as per City of Hope standard operating procedures; schedule of G–CSF administration and PBSC collections can only be ascertained when DAY 0 is identified; when treatment regimen schedule has been fixed and schedule of G–CSF administration and PBSC collections made, schedule has to be confirmed with personnel in apheresis room; DAY 0 should be fixed on a Tuesday–Friday; marrow collection allowed in cases of pediatric donors unable to receive G–CSF due to age, or for donors unable to collect minimum target $CD34^+$ cell dose.

4.8.6 *SUPPLIER:* commercially available; 2 vial sizes, 300 µg/1 ml and 480 µg/1.6 ml; recombinant G–CSF, Filgrastim or Neupogen® (Amgen Inc trademark).

4.8.7 *Refer to NEUPOGEN® (G–CSF, GRANULOCYTE–COLONY STIMULATING FACTOR OR FILGRASTIM) package insert for more information.*

5.0 PATIENT SELECTION Ω §§ B.001, C.001, H.003

Patients with LG, IG and MCL NHL with inability to collect adequate numbers of SCs, failed previous therapies or autologous transplant, or who have multiple relapses and are unlikely to benefit from an autologous transplant will be screened for this study. Patients with MCL in first PR or CR, or in any disease state will also be evaluated for this study.

5.1 INCLUSION CRITERIA Ω §§ C.001, H.003

5.1.1 Age ≥ 18 and < 70 years

5.1.2 6/6 HLA matched sibling donor or related donor, or acceptable matched unrelated donor

5.1.3 Biopsy (Bx) proven diagnosis of LG (including SLL/CLL, lymphoplasmacytic lymphoma, marginal zone, MALT lymphoma and FL grade 1 and 2), IG (FL grade 3 and DLCL) or MCL NHL

5.1.4 Prior demonstrated monoclonal $CD20^+$ malignant B–Cell population in lymph nodes and/or BM Bx specimen

5.1.5 LG NHL; must have relapsed after achieving a CR or PR to prior therapy or have never responded to prior therapy, including chemotherapy and/or MAb therapy.

5.1.6 MCL NHL in any disease state.

5.1.7 Other aggressive B-cell lymphomas (excluding Burkitt lymphoma or Burkitt-like lymphoma) having had at least one relapse or having been refractory to chemotherapy.

5.1.8 BM aspiration and Bx (≤ 42 days prior to imaging dose) which show < 25% lymphomatous involvement of total cellularity; in CLL, peripheral lymphocyte count < 5000/mm^3

5.1.9 Salvage chemotherapy/MAbs to reduce BM lymphomatous involvement and reduce disease bulk allowed.

5.1.10 Normal renal function test with serum creatinine of ≤ 1.5 mg/dl, or a creatinine clearance of ≥ 60 ml/min

5.1.11 Adequate pulmonary function as measured by FEV1 > 65% of predicted measured, or a DLCO ≥ 50% of predicted measured

5.1.12 Cardiac Ejection fraction of > 50% by Echocardiogram (ECHO) or MUGA

5.1.13 Adequate liver function tests with a bilirubin of ≤ 1.5x normal and SGOT or SGPT ≤ 2x normal

5.1.14 Negative Human Immunodeficiency Virus (HIV) antibody

5.1.15 *KPS* > 80

5.1.16 No active Central Nervous System (CNS) disease or prior history of CNS disease

5.1.17 Involved field External Beam Therapy (EBT) to area excluding lung, heart, liver and kidney allowed, but evaluated on a case–by–case basis.

5.1.18 Recovery from last therapy and therapy dose (Y-90 Zevalin) must be ≥ 4 weeks from prior systemic chemotherapy

5.2 EXCLUSION CRITERIA Ω §§ C.001, H.003

5.2.1 Presence of Human Anti–Zevalin® Antibody (HAZA)

5.2.2 Prior RIT

5.2.3 Prior AHSCT; but prior aHSCT is allowed; Prior FTBI in the conditioning regimen will be evaluated on an individual basis.

5.2.4 Prior malignancy, except for: adequately treated basal cell or squamous cell skin cancer; adequately treated noninvasive carcinomas; or other cancer from which the patient has been disease–free for at least 5 years. MDS is excluded from this criterion.

5.2.5 Active evidence of Hepatitis B or C infection; Hepatitis B surface antigen positive.

5.2.6 Total peripheral lymphocyte count > 5,000/mm^3 if SLL/CLL

5.2.7 Burkitt lymphoma or Burkitt-like lymphoma

5.3 DONOR SELECTION Ω §§ B.001, H.003

5.3.1 INCLUSION CRITERIA

5.3.1.1 Age < 75 years

5.3.1.2 HLA genotypically identical related donor or acceptable matched unrelated donor

5.3.1.3 Must consent to G–CSF administration and leukapheresis for matched sibling donor, but for unrelated donor, the donor will sign a standard consent for donation at their designated donor or collection center.

5.3.1.4 Must have adequate veins for leukapheresis or agree to placement of Central Venous Catheter [CVC (femoral, subclavian)]

5.3.2 EXCLUSION CRITERIA

5.3.2.1 Age < 12 years

5.3.2.2 Identical twin

5.3.2.3 Pregnancy

5.3.2.4 HIV Infection

5.3.2.5 Inability to achieve adequate venous access

5.3.2.6 Known allergy to G–CSF

5.3.2.7 Current serious systemic illness or any disease that may preclude the use of G–CSF (eg, recent thromboembotic event); for unrelated donors, considered ineligible by NMDP donor evaluation center

5.4 GENDER AND MINORITY INCLUSIONS AT CITY OF HOPE NATIONAL MEDICAL CENTER (COHNMC) Ω §§ A.003, A.011, B.001, C.001

5.4.1 PLANNED GENDER AND MINORITY INCLUSION FOR TRANSPLANT PATIENTS WITH LYMPHOMA

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	White, Hispanic or not–Hispanic Unknown	Other or Unknown	Total
Female	0%	9%	4%	16%	54%	17%	0%	100%
Male	0%	5%	2%	20%	60%	12%	1%	100%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%

6.0 STUDY DESIGN Ω §§ A.011, A.012, J.001– J.003

This is a single center Phase II trial. Registration will be done at COHNMC according to *§ 14.2 REGISTRATION GUIDELINES*. Prior to ^{90}Y–Zevalin® treatment, patients are required to undergo an imaging scan to verify that they have a favorable biodistribution. Study design considerations and targeted response rates are found in *§ 15.0 STATISTICAL CONSIDERATIONS*. Patients will receive ^{90}Y–Zevalin® to deliver 0.4 mCi/kg, Fludarabine 125 mg/m^2, Melphalan 140 mg/m^2

6.1 Toxicity Grading and Reporting Ω §§ J.001– J.003

Toxicities will be graded using the *National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP)* Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) which can be found at: http://ctep.cancer.gov/reporting/ctc.html and the Modified Bearman Toxicity Scale (Appendix I). The Modified Bearman Toxicity Scale will be used up to day 100 post transplant. Adverse events will be reported according to *Adverse Event Reporting Requirements for Clinical Trials: Policies and Procedures of the City of Hope (City of Hope National Medical Center and Beckman Research Institute) November 2003* found at http://www.coh.org/irb/Documents/irb3810.doc. To be evaluable for toxicity a patient must receive a complete course of treatment and be observed for at least 90 days after the administration of the ^{90}Y. Patients without a durable graft at 90 days, but otherwise not qualifying as graft failure, have up to 100 days to document a durable graft before being considered a graft failure. All patients who are not evaluable for toxicity will be replaced. Toxicities observed will be summarized in terms of type (organ affected or laboratory determination), severity (by NCI CTC and nadir or maximum values for the laboratory measure) and time of onset. For grade 4 neutropenia, duration will be recorded.

6.1.1 *Definition of Graft Durability* – maintenance of normal blood counts at 100 days, 6 months, and 12 months post–transplantation according to the following criteria*:*

6.1.1.1 PLT count > 50,000 (50 x 10^9/l) without transfusion for at least 2 weeks prior to the follow–up visit.

6.1.1.2 Hemoglobin level ≥ 10 g/dl with no erythropoietin or transfusions for at least 2 weeks prior to the follow–up visit.

6.1.1.3 ANC > 1,000 (1 x 10^9/l) with no G–CSF for at least 1 week prior to the follow–up visit.

6.1.2 *Definition of Graft Failure* – confirmation of one or both of the following*:*

6.1.2.1 No durable graft in 2 cell lines of red blood cells, leukocytes, and PLTs (using definitions of durability above) at 100 days post–transplantation with no evidence of other causes, such as recurrent progressive leukemia, renal failure, chronic bleeding, severe infection, drug–induced cytopenias or development of new hematologic problems (nutritional or otherwise).

6.1.2.2 ANC < 500 (0.5 x 10^9/1) by 28 days post–transplantation.

7.0 TREATMENT PLAN Ω §§ A.011–A.012, B.002–B.006, C.002, D.001–D.013, E.002–E.003, E.006, F.001–F.011, G.001–G.005, H.001–H.002

7.1 *TREATMENT SCHEMA* Ω §§ A.011–A.012, B.002–B.006, C.002, D.001–D.013, E.002–E.003, E.006, F.001–F.011, G.001–G.002, H.001–H.002

OUTLINE OF PREPARATIVE REGIMEN (REDUCED INTENSITY CONDITIONING (RIC))

Day -23 or -22:	Blood draw for Rituxan level (see note below figure 7.1.1)
Day –21:	RII with 111In–Zevalin® (per §§ 7.2.1.1, 7.2.1.2, 7.2.1.5) following 250 mg/m2 Rituxan or no Rituxan (depending on Rituxan level drawn on day -23 or -22; refer to table guide below fig. 7.1.1)
Day -16 or -15:	Blood draw for Rituxan level (see note below figure 7.1.1)
Day –14:	RIT with 90Y–Zevalin® per §§ 7.2.1.3, 7.2.1.4, 7.2.1.5 following 250 mg/m2 Rituxan or no Rituxan (depending on Rituxan level drawn on day -16 or -15; refer to table guide below fig. 7.1.1)
Days –9 to –5:	Fludarabine Administration per § 7.2.2.1 (given outpatient if possible)
Day –4:	Melphalan Administration per § 7.2.2.2 (given inpatient)
Days–3 to +30:	Tacrolimus and Sirolimus per §§ 7.3.1, 7.3.2, 7.8 (GVHD prophylaxis)
Days +1, +3, +6:	Mini-MTX GVHD prophylaxis (for certain pts as per COH SOP G.001.04) http://www.coh.org/hct-sop/Section%20G/G.001.04_Acute_Graft_versus_Host_Prophylaxis.pdf and http://www.coh.org/hct-sop/Section%20G/G.001.04_Acute_Graft_versus_Host_Addendum_A.pdf (accessibility verified 04/01/10)

Days –4 to 0:	Granulocyte–Colony Stimulating Factor (G–CSF) Administration to Donor per § 7.4.1
Days –1 to 0:	Hematopoietic Stem Cell (PBSC) Collection from Donor per § 7.4.2
Day 0:	Allogeneic Hematopoietic Stem Cell Transplant (AHSCT) per § 7.5
Day +1:	Possible Rituxan 250 mg/m2 (refer to guide table below fig. 7.1.2).
Day +8	Rituxan 250 mg/m2 (this will be administered regardless of previous Rituxan doses)

Figure 7.1.1

Day -23 or -22 Rituxan level	Give Day -21 Rituxan?	Day -16 or -15 Rituxan level	Give Day -14 Rituxan?
≥ 10 μg/ml	No	≥ 10 μg/ml	No
< 10 μg/ml	Yes	< 10 μg/ml	Yes

NOTE: On Monday holidays, the Rituxan level will be drawn the Friday before. If the level is ≥15 μg/ml, another sample on Monday does not need to be drawn (because the level will not have decreased to < 10 μg/ml by Monday). Additionally, if the value is <10 μg/ml, another sample on Monday again does not need to be drawn (because the patient will be receiving Rituxan according to the table above). However, if the value is ≥10 μg/ml but < 15 μg/ml, then a Rituxan level draw will be repeated on Monday.

Figure 7.1.2

Received Rituxan Day -21?	Received Rituxan Day -14?	Give Rituxan Day +1?	Give Rituxan Day +8?
No	No	Yes	Yes
Yes	Yes	No	Yes
Yes	No	No	Yes
No	Yes	No	Yes

7.2 REDUCED INTENSITY CONDITIONING (RIC) REGIMEN Ω §§ C.002, E.002–E.003, E.006, F.001–F.011, G.001–G.002

7.2.1 RADIOIMMUNOTHERAPY (OUTPATIENT)

On DAY –21, patients will receive the fixed dose of approximately 5.0 mCi ^{111}In–Zevalin® possibly preceded by an initial infusion of 250 mg/m^2 Rituxan®; on DAY –14, patients will receive 0.4 mCi/kg ^{90}Y–Zevalin®, possibly preceded by an initial infusion of 250 mg/m^2 Rituxan®. The day -21 and day -14 Rituxan dosing is based on the Rituxan levels in the blood which will be drawn on day -23 or -22 (for the imaging dose), and on day -16 or -15 (for the therapy dose) [See figure 7.1.1 above].

7.2.1.1 RITUXAN® (DAY OF IMAGING): on DAY –21, if Rituxan® is given, it will be administered by slow iv infusion having been diluted to 1–4 mg/ml in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. This initial Rituxan® infusion will be through a dedicated line. If patient has had Rituxan before, begin infusion at 100 mg/hr. If no adverse reactions occur, escalate rate gradually at 100 mg/hr every 30 minutes to a maximum of 400 mg/hr. If patient has not had Rituxan before, begin infusion at 50 mg/hr. If no adverse reactions occur, escalate rate at 50 mg/hr every 30 minutes to a maximum of 400 mg/hr. If hypersensitivity or infusion related events develop, the infusion will be temporarily slowed or interrupted. The infusion can be continued at half the previous rate when symptoms abate.

Note: prior to the start of Rituxan infusion, blood samples (1 EDTA purple top tube and 1 red top tube) will be obtained for analysis of antibody clearance (see 7.2.1.2).

7.2.1.2 *^{111}IN–ZEVALIN® IMAGING:* following the Rituxan® infusion, if given, ^{111}In–Zevalin® will be administered over approximately 10 minutes by slow IV injection. A 0.22 micron filter will be on the line between the patient and the infusion port. The line will be flushed with at least 10 mls of normal saline following the ^{111}In–Zevalin® infusion.

Whole body gamma camera images will be obtained at approximately 1–24 hours, approximately 48–72 hours and an optional third scan at approximately 90–120 hours post–infusion to confirm results. Exceptions to this time frame will be made if the optional scan falls on a weekend or a holiday. Spot planar views and SPECT scans may be obtained at the discretion of the PI or Co-PI. Blood samples (1 EDTA purple top tube and 1 red top tube) will be obtained at approximately time 0 (pre-Rituxan, if given, and pre-In-111-Zevalin), 2 hours, 4–6 hours, 1 day, 2 days, 3-4 days, 5 days and 6 days post–infusion of the antibody, if available. These samples will be used for analysis of antibody clearance and bone marrow dose estimation. Urine samples will be collected daily for 6 days for analysis of radioisotope clearance, if available. Results will provide investigators a means to evaluate toxicities.

Patients *with unfavorable biodistribution* (eg, localization to the spleen and/or failure of isotope to clear kidneys) indicating increased toxicities and unacceptable risks will be taken off study, not to proceed with ^{90}Y–Zevalin® RIT. If patients *do not show unfavorable biodistribution*, ^{90}Y–Zevalin® will be administered on DAY –14.

7.2.1.3 *RITUXAN® (DAY OF THERAPY):* on DAY –14, if Rituxan® is given, it will be administered by slow iv infusion having been diluted to 1–4 mg/ml in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. This second Rituxan® infusion will be through a dedicated line at a rate of 100 mg/hr. If hypersensitivity or infusion–related events do not occur, the infusion will be escalated at a rate of 100 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If hypersensitivity or infusion related events develop, the infusion will be temporarily slowed or interrupted. The infusion can be continued at half the previous rate when symptoms abate.

7.2.1.4 *^{90}Y–ZEVALIN® THERAPY:* following the Rituxan® infusion, if given, 0.4 mCi/kg of ^{90}Y–Zevalin® will be administered over approximately 10 minutes by slow IV injection. A 0.22 micron filter will be on the line between the patient and the infusion port. The line will be flushed with at least 10 mls of normal saline following the ^{90}Y–Zevalin® infusion.

7.2.1.5 *PRODUCT DOSE AND SCHEDULE*

7.2.1.5.1 *RITUXAN®*

7.2.1.5.1.1 *DAY –21:* 250 mg/m^2 (if given, see figure 7.1.1)

7.2.1.5.1.2 *DAY –14:* 250 mg/m^2 (if given, see figure 7.1.1)

7.2.1.5.1.3 *Day +1:* 250 mg/m^2 (if given, see figure 7.1.2)

7.2.1.5.1.4 *Day +8:* 250 mg/m^2

7.2.1.5.2 *^{111}IN–ZEVALIN® and ^{90}Y–ZEVALIN®:* An ^{111}In and ^{90}Y isotope order form will be completed and faxed to the designated isotope vendor prior to RII/RIT. Dosing of *ZEVALIN®:*

7.2.1.5.2.1 *^{111}IN–ZEVALIN®:* 5.0 mCi fixed dose.

7.2.1.5.2.2 *^{90}Y–ZEVALIN®:* 0.4 mCi ^{90}Y/kg. Dose will be calculated using patient's actual body weight at time of baseline evaluation **[NOT TO EXCEED 32 MCI (MAXIMUM DOSE) +/- 20% PER NUCLEAR REGULATORY COMMISSION GUIDELINES]**.

7.2.2 *CHEMOTHERAPY (Fludarabine to be given OUTPATIENT if possible. Melphalan given INPATIENT)*

7.2.2.1 *DAYS –9 TO –5 FLUDARABINE:* 25 mg/m^2/day iv; based on actual body weight, given outpatient if possible.

7.2.2.2 *DAY –4 MELPHALAN:* 140 mg/m^2 iv; based on actual body weight.

7.3 IMMUNOSUPPRESSION [Graft–VERSUS–HOST–DISEASE (GVHD) PROPHYLAXIS] Ω §§ E.002–E.003, G.001– G.002, G004

7.3.1 *DAY –3 TACROLIMUS TREATMENT:* commence Tacrolimus at 0.02 mg/kg iv daily until oral intake resumes; then switch to oral at 2–3x the iv dose and taper based on disease status as described in *§ 7.8 GUIDELINES FOR TAPERING IMMUNOSUPPRESSION*. Dosing of Tacrolimus will be based on adjusted ideal body weight; if actual body weight is < ideal body weight, then actual body weight will be used.

7.3.1.1 *GUIDELINES FOR TACROLIMUS DOSE ADJUSTMENT AND MANAGEMENT OF TOXICITIES:* if vomiting occurs in ≤ 20 minutes after an oral dose of Tacrolimus, the dose should be repeated. Anti–nausea medications may be given as needed. Intractable nausea and vomiting may require intravenous administration of Tacrolimus at one third the oral dose. Tacrolimus may cause impaired renal function, hyperbilirubinemia, increased serum transaminase levels, hypertension, tremor, and seizures. Impaired renal function may require Tacrolimus dose reductions. Tacrolimus treatment may be *DISCONTINUED, INTERRUPTED* or *SUSPENDED* at any time for patient refusal to continue treatment, severe drug related toxicity or Serious Adverse Event (SAE).

Tacrolimus dose adjustments should not be based exclusively on serum levels. Tacrolimus levels should be used as a guide in conjunction with clinical observations of the biologic effects of the drug, (ie, toxicity and immunosuppression). Blood pressure, renal function tests (creatinine, BUN), electrolytes and magnesium need to be followed at least 3x/week while receiving Tacrolimus at full dose and then twice weekly or per attending until Tacrolimus is discontinued.

SUGGESTED TACROLIMUS DOSE ADJUSTMENT GUIDELINES

PLASMA LEVELS	TOXICITY GRADE	TACROLIMUS DOSE
< 5 ng/ml	0	↑ 25%
5–10 ng/ml	0, I	No change
5–10 ng/ml	II	↓ 25%
5–10 ng/ml	III	↓ 50%
5–10 ng/ml	IV	Stop 100%
10-15 ng/ml	0	↓ 25% every 3–4 days
>15 ng/ml	0	Hold x 24 hrs, then restart at ↓ 25%

7.3.1.2 *TACROLIMUS BLOOD LEVELS:* Tacrolimus trough levels should be measured at least weekly during the first 50 days post–transplant. Target levels of 5–10 ng/ml are acceptable in patients who manifest no evidence of toxicity or GVHD. Trough plasma levels should be drawn 10–12 hours after the last dose if possible.

7.3.1.3 *TACROLIMUS DRUG INTERACTIONS*

7.3.1.3.1 Drugs that may *INCREASE* Tacrolimus levels: Fluconazole, Itraconazole, Ketoconazole, erythromycin, H2 Blockers, Verapamil, Diltiazem, Nicardipine, Danazol, Bromocriptine, Metoclopramide, Methylprednisolone, Somatostatin (Octreotide).

7.3.1.3.2 Drugs that may *DECREASE* Tacrolimus levels: Rifampin, Phenobarbital, Phenytoin, Carbamazepine, Octreotide (may lower Serum Levels by *DECREASING* Intestinal Absorption of the Oral Drug).

7.3.1.3.3 Drugs that may result in *ADDITIVE* Nephrotoxicity: Aminoglycosides, Amphotericin B, Acyclovir, Furosemide, Trimethoprim–Sulfamethoxazole (TMP–SMX).

7.3.2 *DAY –3 SIROLIMUS TREATMENT:* Sirolimus will be administered at 12 mg orally loading dose on DAY –3, followed by 4 mg orally single morning daily dose (target serum level 3–12 ng/ml by HPLC). Dosing of Sirolimus will be based on adjusted ideal body weight. If actual body weight is < ideal body weight, actual body weight will be used. Taper or continue based on disease status as described in *§ 7.8 GUIDELINES FOR TAPERING IMMUNOSUPPRESSION.*

7.3.2.1 *GUIDELINES FOR SIROLIMUS DOSE ADJUSTMENT AND MANAGEMENT OF TOXICITIES:* dose adjustments are based on clinical toxicity, blood levels, GVHD and clinical judgment involving the rate of rise or decline of the serum level. For levels < 3 ng/ml, it is suggested that the dose be increased by approximately 25% increments no more frequently than every 2 days, rounded to the nearest full milligram until the target range is achieved. Conversely, for levels > 12 ng/ml, it is suggested that the dose be decreased by ~25% no more frequently than every 2 days until the target level is achieved. If vomiting occurs ≤ 20 minutes of administration the dose should be repeated. Anti–nausea medication may be given as needed.

Sirolimus treatment may be *DISCONTINUED, INTERRUPTED* or *SUSPENDED* at any time for patient refusal to continue treatment or drug related SAE *(§§ 11.0 EXTERNAL REGULATORY REQUIREMENTS and 12.0 INTERNAL REGULATORY REQUIREMENTS)*. The most serious reported SAEs from Sirolimus in previous clinical studies after HSCT included hyperlipidemia, hypertension, rash, thrombocytopenia, leukopenia, arthralgias, diarrhea and HUS.

For management of cytopenias, it is recommended that patients receive growth factors or transfusions if necessary. For patients with HUS (defined as presence of microangiopathy and rise in serum creatinine > 2x upper limit of normal, not attributed to other causes), Sirolimus should be adjusted to maintain therapeutic levels; discontinuation of Tacrolimus is recommended in this setting, particularly for cases requiring hemodialysis, seizures or severe hemolysis. Plasmapheresis may be used at the discretion of the treating physician. No dose modification is recommended for hyperlipidemia; lipid–lowering agents should be instituted, with careful attention to the occurrence of rhabdomyolysis when HMGCoA reductase inhibitors are used.

Sirolimus treatment may also be interrupted for inability to swallow due to stomatitis; for patients with severe stomatitis who may not be able to resume oral intake in several days, MMF may be started as GVHD prophylaxis, at a dose of 15 mg/kg intravenously twice a day, until oral intake resumes, when Sirolimus may substitute MMF.

Sirolimus should be adjusted for hepatic impairment, as follows: for bilirubin > 2.0, reduce maintenance dose by 30%. Sirolimus may be re–instituted if, in the judgment of the investigator, the primary clinical cause(s) for dose adjustment have been resolved.

7.3.2.2 *SIROLIMUS SERUM LEVELS:* Sirolimus trough levels should be measured at least weekly during the first 50 days post–transplant. Levels of 3–12 ng/ml are considered therapeutic. Trough levels should be measured 20–24 hours after the last dose.

7.3.2.3 *SIROLIMUS DRUG INTERACTIONS:* Sirolimus is a substrate for both cytochrome CYP3A4 and P–glycoprotein.

7.3.2.4 *DRUGS THAT MAY INCREASE SIROLIMUS BLOOD CONCENTRATIONS INCLUDE:*

7.3.2.4.1 *Calcium Channel Blockers:* Diltiazem, Nicardipine, Verapamil

7.3.2.4.2 *Calcineurin Inhibitors:* Cyclosporine

7.3.2.4.3 *Antifungal Agents:* Ketoconazole, Clotrimazole, Fluconazole, Itraconazole

7.3.2.4.4 *Macrolide Antibiotics:* Clarithromycin, Erythromycin, Troleandomycin

7.3.2.4.5 *Gastrointestinal Prokinetic Agents:* Cisapride, Metoclopramide

7.3.2.4.6 *Other Drugs:* Rifampin, Bromocriptine, Cimetidine, Danazol, HIV–Protease Inhibitors (eg, Ritonavir, Indinavir)

7.3.2.4.7 *DUE TO EXTREME INTERACTIONS WITH VORICONAZOLE, THE DOSE OF SIROLIMUS SHOULD BE REDUCED TO 25% WHEN GIVEN WITH VORICONAZOLE.*

7.3.2.5 DRUGS THAT MAY DECREASE SIROLIMUS CONCENTRATIONS INCLUDE:

7.3.2.5.1 *Anticonvulsants:* Carbamazepine, Phenobarbital, Phenytoin

7.3.2.5.2 *Antibiotics:* Rifabutin, Rifapentine

7.3.2.5.3 *Herbal Preparations:* St. John's Wort (Hypericum Perforatum) could result in *REDUCED* Sirolimus Concentrations.

7.3.2.5.4 Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Rapamune®. Grapefruit Juice *REDUCES* CYP3A4–mediated metabolism of Rapamune® and *MUST NOT BE USED FOR DILUTION.*

7.3.3 *DAY* +1, +3, +6 *MINI METHOTREXATE TREATMENT:* Certain patients will receive mini-MTX in addition to Tacrolimus and Sirolimus as part of the acute GVHD prophylaxis regimen as per COH SOP G.001.04, *Acute Graft versus Host Disease Prophylaxis* http://www.coh.org/hct-sop/Section%20G/G.001.04_Acute_Graft_versus_Host_Prophylaxis.pdf and http://www.coh.org/hct-sop/Section%20G/G.001.04_Acute_Graft_versus_Host_Addendum_A.pdf (accessibility verified 04/01/10)

7.4 COLLECTION OF DONOR HEMATOPOIETIC STEM CELLS (PBSCs) Ω §§ B.001–B.005

7.4.1 G–CSF ADMINISTRATION TO DONORS

All donors will receive G–CSF per City of Hope standard operating procedures. G–CSF will be administered by a subcutaneous daily injection. The schedule of G–CSF administration and PBSC collections can only be ascertained when DAY 0 is identified. When a treatment regimen schedule has been fixed and the schedule of G–CSF administration and PBSC collections made this has to be confirmed with the personnel in the apheresis room. DAY 0 will be fixed on a Tuesday–Friday.

7.4.2 PERIPHERAL BLOOD STEM CELLS (PBSC) COLLECTION

The Donor will preferably undergo collections vein–to–vein; or through appropriate CVC inserted on or before day of treatment regimen.

TREATMENT SCHEMA FOR DONOR

Days	-5	–4	–3	–2	–1	0
G–CSF as per COH SOP	X	X	X	X	X	
PBSC collection				X	X	
PBSC infusion						X

PBSCs will be collected in the afternoon of DAY –1, stored in the refrigerator at 4ºC overnight. A second collection may be performed the following afternoon to try to achieve the target cell dose, and both collections will be transfused on DAY 0.

The target dose of PBSCs to be collected will be specified at 5–10 x 10^6 $CD34^+$ cells/kg, with a minimum of 2 x 10^6 $CD34^+$ cells/kg. For donors not achieving a minimum $CD34^+$ cell count of 2 x 10^6/kg after 3 daily collections, BM harvesting may be recommended at the discretion of the treating physician.

If PBSCs cannot be collected by a vein–to–vein technique, a percutaneous Quinton Catheter or its equivalent will be inserted. General procedures will include the use of a standard apheresis machine, and processing ≤ 16 L of whole blood during the collection.

Marrow collection is allowed in the case of pediatric donors unable to receive G-SCF due to age, or for donors unable to collect a minimum target CD34+ cell dose or for donors who are unable to receive G-CSF or refuse to donate PBSC.

In circumstances in which the donor is unable to donate cells on the date requested, cryopreservation of the stem cell product is allowed as per COH SOP.

7.5 HEMATOPOIETIC STEM CELL (PBSC) INFUSION Ω §§ B.006

All patients will receive unmodified G–CSF mobilized PBSCs from an HLA identical related or unrelated donor on DAY 0 of the treatment regimen. For unrelated donor, the stem cell product will either be unmodified G–CSF mobilized PBSCs or bone marrow.

7.6 DONOR LYMPHOCYTE INFUSION (DLI) Ω §§ B.004–B.005, H.001–H.002

DLI will be an option off protocol for subjects who relapse or have persistent disease post transplant. If the patient requires DLI, he/she will be taken off protocol. For aggressive PD after transplant, such that the treating physician believes that the patient cannot wait to undergo DLI, the patient may receive alternative treatments such as chemotherapy or radiation off protocol.

7.7 SUPPORTIVE CARE Ω §§ D.001–D.013, F.001–F.011, G01–G.007

Supportive care will be given as per City of Hope standard operating procedures.

7.7.1 ACCESS TO VESSELS

Prior to admission, during pre–transplant evaluation, all patients will have a permanent CVC placed.

7.7.2 HYPERALIMENTATION

All patients will receive appropriate Hyperalimentation as soon as necessary after admission. The goal will be to prevent even a short duration of negative nitrogen balance.

7.7.3 PLATELET TRANSFUSION

7.7.3.1 *INDICATION.* Platelets are transfused to prevent bleeding and an attempt is made to keep the circulating level > 15–20,000/mm^3 at all times. This goal may be changed by the attending physician as clinically indicated.

7.7.3.2 *IRRADIATION.* All blood products are irradiated with 1,500 cGy prior to infusion.

7.7.4 MANAGEMENT OF FEVER/INFECTIONS

Treatment of patients on this protocol is not intended to restrict the freedom of the managing physician to treat suspected or documented infections. In neutropenic patients, however, the following guidelines will be followed:

7.7.4.1 All febrile, neutropenic patients will be treated with IV antibiotic(s), the choice of which will be guided by the patient's clinical history, institutional practices and subsequent culture results.

7.7.4.2 Patients with documented, invasive fungal infection or with persistent, unexplained fevers while neutropenic and on broad–spectrum antibiotic therapy will receive appropriate antifungal therapy.

7.7.5 POST–TRANSPLANT GROWTH FACTORS

Growth factors will not be given unless severe persistent neutropenia develops or persists past DAY 21 post–transplant (ANC < 100/m^3 for > 5 days).

7.7.6 INFECTION PROPHYLAXIS

Levofloxacin (or non–absorbable oral antibiotics for levofloxacin allergy) for gastrointestinal decontamination will be given in certain cases per treating physician discretion. Otherwise, prophylactic antibiotics will be given per institutional guidelines. TMP–SMX (pentamidine or atovaquone for sulfa allergy) will be administered from DAY –9 to DAY –3 and prophylaxis will be reinstituted when white blood cells are > 3000 and continued until 6 months post–transplant. The choice of TMP–SMX as a prophylactic agent may be altered based on a history or sensitivity to this agent or associated cytopenias. Empiric broad-spectrum antibiotics will be used as clinically indicated, per institutional guidelines. Anti–fungal prophylaxis will be administered beginning on DAY 1 and continued daily until granulocytopenia resolves; continuation of anti–fungal therapy beyond this point will be at the discretion of the treating physician. Herpes prophylaxis with acyclovir for patients with HSV^+ serology will begin on DAY –1. CMV monitoring will commence 21 days post–transplant and continue until 80–100 days post–transplant; treatment for reactivation will be given according to institutional guidelines. Patients may participate in clinical protocol for prevention of infections.

7.8 GUIDELINES FOR TAPERING IMMUNOSUPPRESSION Ω §§ G.001–G.005

Individual tapering of immunosuppression will be at the discretion of the treating physician. In general, no evidence of GVHD should be present and the following guidelines will be observed:

7.8.1 For patients with persistent or progressive disease at 30 days post–transplant, begin simultaneous taper of Tacrolimus and Sirolimus over 2–4 months.

7.8.2 For patients with CR/PR at 30 days post–transplant, begin tapering Tacrolimus and Sirolimus 3–6 months post–AHSCT over 3–6 months as tolerated.

8.0 PATIENT EVALUATIONS Ω §§ A.011–A.012, B.002–B.006, C.002, D.001–D.013, E.002–E.003, E.006, F.001–F.011, G.001–G.005, H.001–H.002

8.1 EVALUATION/TESTS DURING THE ^{111}IN–ZEVALIN® IMAGING PERIOD Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

8.1.1 Vital signs will be obtained approximately every 15 minutes for the first hour during the Rituxan® infusion, approximately hourly during the remainder of the infusion, and approximately every 15 minutes x 4 following the start of ^{111}In–Zevalin® infusion. If vital signs are unstable, they will be monitored approximately at 5 minute intervals until stable.

8.1.2 The purpose of ^{111}In–Zevalin® imaging is twofold:

8.1.2.1 To evaluate biodistribution of whole body γ–camera images.

8.1.2.2 To assess whether biodistribution is acceptable to proceed with ^{90}Y–Zevalin® RIT.

8.1.3 The biodistribution of ^{111}In–Zevalin® is to be determined from a visual evaluation of whole body γ–camera images during the first day (1–24 hours) and the second or third

day (48–72 hours) after injection. A third scan may be taken on the fourth or fifth day (90–120 hours) if needed to confirm results.

8.1.3.1 EXPECTED BIODISTRIBUTION:

8.1.3.1.1 Easily detectable uptake in the blood pool areas (including but not limited to the heart, major abdominal blood vessels, vascular areas of the head, lungs and pelvis) on the first day image, with less activity in the blood pool areas on the second or third day image.

8.1.3.1.2 Moderately high to high uptake in normal liver and spleen during the first day and the second or third day images.

8.1.3.1.3 Moderately low or very low uptake in normal kidneys, urinary bladder, and normal bowel on the first day image and the second or third day image.

8.1.3.1.4 Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor bearing areas in normal organs may be seen as areas of increased or decreased intensity.

8.1.3.2 ALTERED BIODISTRIBUTION

8.1.3.2.1 Diffuse uptake in normal lung more intense than the cardiac blood pool on the first day image, or more intense than the liver on the second or third day image.

8.1.3.2.2 Kidneys with greater intensity than the liver on the posterior view of the second or third day image.

8.1.3.2.3 Intense areas of uptake throughout the normal bowel comparable to the liver on the second or third day images.

8.1.4 Biodistribution of ^{111}In–Zevalin® will be assessed on the first day image and second or third day image. If desired, a third image may be obtained at 90–120 hours to support the decision. If the patient has an altered biodistribution, the patient will be taken off study before proceeding to ^{90}Y–Zevalin® RIT.

8.2 EVALUATIONS/TESTS DURING THE ^{90}Y–ZEVALIN® TREATMENT PERIOD UP TO MONTH 3 Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

8.2.1 Vital signs will be obtained approximately every 15 minutes for the first hour during the Rituxan® infusion, approximately hourly during the remainder of the infusion, and approximately every 15 minutes x 4 following the start of ^{90}Y–Zevalin® infusion. If vital signs are unstable, they will be monitored approximately at 5-minute intervals until stable.

9.0 STUDY CALENDAR Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

9.1 STUDY CALENDAR — PRE–STUDY THROUGH DAY 0 (TRANSPLANT DAY) Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

REQUIRED STUDIES	PRE–STUDY[1]	DAY -23 OR -22	DAY –21	DAY -16 OR -15	DAY –14	DAY –9	DAY –8	DAY -7	DAY –6	DAY –5	DAY –4	DAY –3	DAY –2	DAY –1	DAY 0
PHYSICAL															
H and PE with KPS	X														
LABORATORY															
CBC & PLT	X[3]					X[5]					X	X	X	X	X
WBC Differential	X[3]					X[5]									
Reticulocyte Count	X														
HAZA@	X#														
Comprehensive Metabolic Panel, LDH	X					X[5]									
Basic Metabolic Panel											X	X	X	X	X
PT/PTT	X														
ABO/Rh Typing	X														
B2 Microglobulin	X														
Quantitative Igs	X														
Urinalysis	X														
CMV Titer	X														
HSV Titer	X														
Hepatitis Panel (incl Hep B surf Ag)	X														
HIV Antibody	X														
Eval & Rx of CNS Dz if indicated (pts w/BM inv w/large cell NHL, testicular inv or neurologic sx)	X														
Unilateral Bone Marrow Aspiration/Biopsy*	X														
Creatinine Clearance	X														
10 cc Sodium Heparin Blood to HLA Laboratory for DNA Storage	X														
Blood draw for RTX level		X		X											
Costim Assays[2]		X					X[4]								
DIAGNOSTIC TESTS/RADIOLOGY															
EKG	X														
ECHO	X														
DLCO/FEV1	X														
CXR	X														
CT scans NCAP	X														
FDG–PET Scan as indicated	X														
TREATMENT															
Rituxan®			X%		X%										
^{111}In–Zevalin®+			X												
^{90}Y–Zevalin®					X										
Bactrim or Equivalent						X	X	X	X	X	X	X			
Fludarabine						X	X	X	X	X					
Melphalan											X				
Acyclovir														X	
Allo–HSC Infusion**															X
Commence Tacrolimus$												X	X	X	X
Commence Sirolimus^												X	X	X	X

Serum must be drawn ≤4 wks prior to imaging dose. Results are required prior to enrollment for those pts who have been prev rx w/murine proteins including Rituxan®.

* Send for morphology, flow cytometry, and cytogenetics. Whenever possible, for patients with MCL, and patients with a history of peripheral blood involvement by follicular lymphoma, PCR gene rearrangement studies for bcl-1 or bcl-2 will be done. (PCR may be done on PB or BM).

\+ Including dosimetry studies.

3 for pts with CLL or PB involvement, CBC, Diff & PLT to be done ≤ 1 wk prior to imaging dose.

@ Draw at least 5 ml blood into a red top tube. Deliver specimen to the RIT lab.

1 All pre-study tests must be done ≤42 days prior to start of treatment (imaging dose).

$ Tacrolimus tapered as described in § 7.3 of protocol

^ Sirolimus tapered as described in § 7.3 of protocol

% If required per protocol, see table, figure 7.1.1.

** For sibling/related donor HSC only: send approx. 1 ml of the HSC product to the Virology Lab, Familian Science Bldg., Room C209D (x68419). The sample will be obtained at the end of HSC collection (a segment of the collection tubing will be heat sealed and removed for transport). Donor consent will be obtained. Note: this sample will not be collected for MUDs. **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED**.

2 Draw two 6 ml sodium heparin green top tubes, AND two 4 ml sodium heparin green top tubes for an amount of whole blood of about 20 ml and send to Virology Lab, Familian Science Bldg., Room C209D (x68419). **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED**.

4 Day -8 costim draw may be done +/- 2 days. **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED**.

5 +/- 3 days.

9.2 STUDY CALENDAR — DAY 1 THROUGH DAY 84 POST–TRANSPLANT Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

REQUIRED STUDIES	DAY 1	DAY 7[5]	DAY 8	DAY 14[5]	DAY 21[5]	DAY 28[3]	WK 6[3]	WK 8[3]	WK 10[3]	WK 12[3]
PHYSICAL										
H and PE with KPS[11]				X		X		X		X
Acute GVHD Monitoring				X	X	X	X	X		X
LABORATORY										
CBC/PLT[1,9]	X	X		X	X	X	X	X	X	X
WBC Differential[7,9]				X	X	X	X	X	X	X
HAZA[10]								X		
Comprehensive Metabolic Panel, LDH, Mg[8,9]		X		X	X	X	X	X	X	X
Quantitative Igs						X		X		X
CMV Culture or PCR[#]					X	X	X	X		X
Unilateral Bone Marrow Aspiration/Biopsy* (see note bottom of section 9.3)						X[+]				
Chimerism on PB or bone marrow with STR, Q-PCR or sex chromosomes						X				
Costim Assays[2]					X	X		X		
RADIOLOGY										
CT Scans (N)CAP							X[6,&,4]			
FDG–PET/CT Scan							X[6,4]			
TREATMENT										
Rituxan	X**		X							
Commence Anti–Fungal Prophylaxis[%]	X	X		X						
Trimethroprim–Sulfamethoxazole[@]										
Continue Tacrolimus[$]	X	X		X	X	X				
Continue Sirolimus^	X	X		X	X	X				

@ Trimethoprim–Sulfamethoxazole Prophy will be reinstituted when WBC > 3000 & continued through month 6 unless pt has sensitivity to this agent.

% Anti–Fungal Prophylaxis will be administered on DAY 1 and continued daily until granulocytopenia resolves.

$ Tacrolimus will continue daily and taper as described in § 7.3 of protocol

^ Sirolimus will continue daily and taper as described in § 7.3 of protocol

* Send for morphology, flow cytometry, cytogenetics and engraftment studies. Whenever possible, for patients with MCL, and patients with a history of peripheral blood involvement by follicular lymphoma, PCR gene rearrangement studies for bcl-1/bcl-2 will be done.

1 Daily from DAY 0 until discharge.

3 +/– 1 week

5 +/– 4 days

6 For pts whose PET scan prior to conditioning showed no lymphomatous involvement, the week 6 CT & FDG-PET are not required. For patients with CLL/SLL, restaging scans at week 6 are not required.

& At wk 6, separate diagnostic CT only if indicated.

7 Differential will be done daily from day 14 to day 21, as long as the patient is inpatient on those days.

8 To be done weekly until discharge.

9 CBC, DIFF, PLT, CMP, LDH and mg to be done twice a week after discharge until day 90-100.

10 Draw at least 5 ml blood into a red top tube. Deliver specimen to the lab in RIT.

At least weekly up to day 80-100, or per COH SOP F.007.003: http://www.coh.org/hct-sop/Section%20F/F.007.03_Cytomegalovirus_Surveillance,_Prophylaxis_and_Therapy_Guidelines_rev._11.11.09.pdf (accessibility verified 04/01/10)

+ Only required for pts who have BM involvement by lymphoma at study enrollment. (see note bottom of section 9.3)

** If required per protocol, see table, figure 7.1.2.

2 Draw two 6 ml sodium heparin green top tubes, AND two 4 ml sodium heparin green top tubes for an amount of whole blood of about 20 ml and send to Virology Lab Familian Science Bldg, Room C209D (x68419). **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED**.

4 +/- 2 weeks.

11 KPS will not be required when subjects are inpatient.

9.3 STUDY CALENDAR — DAY 90 THROUGH YEAR 5 POST–TRANSPLANT FOLLOW–UP Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

REQUIRED STUDIES	DAY 90–100[3]	DAY 120[3]	MO 6[%]	MO 9[%]	MO 12 (1 YR)[4]	MO 18[4]	MO 24 (YR 2)[4]	MO 30[4]	MO 36 (YR 3)[4]	MO 42[4]	MO 48 (YR 4)[4]	MO 54[4]	MO 60 (YR 5)[4]
PHYSICAL													
H and PE with KPS[11]	X		X	X	X	X	X	X	X	X	X	X	X
Chronic GVHD Monitoring	X		X	X	X	X	X	X	X	X	X	X	X
LABORATORY													
HAZA[@]	X		X		X								
CBC, Diff, Platelets	X		X	X	X	X	X		X				X
Comprehensive Metabolic Panel, LDH, Mg	X		X	X	X	X	X		X				X
B2 Microglobulin	X		X		X	X	X						X
PCR Gene Rearrangement Studies on PB (BCL-1/BCL-2)[5]	X		X		X	X	X						X
Unilateral Bone Marrow Aspiration/Biopsy* (see note below)	X[&]		X[+]		X		X						X
Chimerism on PB or bone marrow with STR, Q-PCR or sex chromosomes	X		X		X[$]								
Costim Assays[2]	X												
CD137 (4-1BB) expression**		X	X										
DIAGNOSTIC TESTS/ RADIOLOGY													
EKG			X		X								
ECHO					X								
DLCO/FEV1					X								
CXR (PA & Lateral) or CT chest	X												
CT Scans (N)CAP[#]	X^		X		X		X						X
FDG–PET Scan if indicated[#]	X^		X		X		X						X

* send for morphology, flow cytometry, cytogenetics, and engraftment studies. Whenever possible, for patients with MCL, and patients with a history of peripheral blood involvement by follicular lymphoma, PCR gene rearrangement studies for bcl-1/bcl-2 will be done. (Engraftment studies are not required after year 1. Note that engraftment studies can be done on either bone marrow or peripheral blood.)

[3] +/– 2 weeks [11] KPS will not be required when subjects are inpatient.

[%] +/- 1 month

[4] +/-2 months

[@] draw at least 5 ml blood into a red top tube. Deliver specimen to the lab in RIT.

[+] BM exam only required at month 6 if the BM exam at day 100 was positive.

[$] as clinically indicated thereafter.

[#] preferably, both a CT and FDG-PET will be done, however, either is acceptable at all of these time points. Note: for patients with CLL/SLL, CT should be done at 6 months and 1 year, PET not required at these time points unless transformation to large cell.

[&] Bone marrow examination is only required at day 90-100 if the bone marrow exam at day 28 was positive.

^ Not necessary if the week 6 exam showed no lymphomatous involvement. For patients with CLL/SLL, restaging scans at day 100 are not required.

[2] Draw two 6 ml sodium heparin green top tubes, AND two 4 ml sodium heparin green top tubes for an amount of whole blood of about 20 ml and send to Virology Lab Familian Science Bldg, Room C209D (x68419). **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED**.

** Draw about 25-30 ml (4 green top tubes) and send to Weimin Tsai, FOX South (x63199). **DUE TO FUNDING, PATIENTS ENROLLED AFTER 6/20/12 WILL NOT HAVE THIS PROCEDURE PERFORMED**.

[5] Whenever possible, for patients with MCL, and patients with a history of peripheral blood involvement by follicular lymphoma.

NOTE: Bone marrow examinations post transplant will be done following these parameters:

- For pts who have had previous bone marrow involvement by lymphoma: do at YR1, YR2, and YR5.
- For pts who have bone marrow involvement by lymphoma at study enrollment: do at d28, d100 (if pos at d28), M6 (if pos at d100), YR1, YR2, and YR5.
- For pts who have never had bone marrow involvement by lymphoma: recommend to do at YR1, YR2, and YR5, as clinically indicated.

10.0 MEASUREMENT OF EFFECT Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

10.1 STAGING CRITERIA Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

Staging of disease must be evaluated ≥ 28 days after the end of the last chemotherapy and ≤ 42 days prior to transplant. Ann Arbor Staging Criteria will be used. Stage is determined based on extent of disease at the time of diagnosis.

ANN ARBOR CLASSIFICATION

STAGE I	Involvement of a single lymph node region (1) or a single extralymphatic organ or site (1); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma).
STAGE II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm(IIE).
STAGE III	Involvement of lymph node regions on both sides of the diaphragm (III) which may be accompanied by localized involvement of an associated extralymphatic organ or site (III_E) or spleen (III_S) or both (III_{SE}).
STAGE IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Any involvement of the liver or bone marrow, or nodular involvement of the lung(s).

A = Asymptomatic
B = Fever, sweats, weight loss > 10% of body weight

10.2 Criteria for Evaluations & Endpoint Definitions

Revised Response Criteria for Malignant Lymphoma α Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

10.2.1 *SENSITIVITY OF DISEASE:* patients are grouped into 1 of 3 groups based on sensitivity of disease:

10.2.1.1 *INDUCTION FAILURE:* patients who did not achieve a *CR* or *PR* from induction chemotherapy.

10.2.1.2 *RESISTANT RELAPSE:* patients who did not achieve a *CR* or *PR* from the most recent standard salvage chemotherapy.

10.2.1.3 *SENSITIVE RELAPSE:* patients who did achieve a *CR* or *PR* from the most recent standard salvage chemotherapy.

10.2.2 *MEASURABLE DISEASE:* tumor that can be accurately measured in size. This information can be used to judge response to treatment.

α *REFERENCE:* BRUCE D. CHESON, BEATE PFSTNER, MALIK E. JUWEID, RANDY D. GASCOYNE, LENA SPECHT, SANDRA J. HORNING, BETRAND COIFFIER, RICHARD I. FISHER, ANTON HAGENBEEK, EMANUELE ZUCCA, STEVEN T. ROSEN, SIGRID STROOBANTS, T.ANDREW LISTER, RICHARD T. HOPPE, MARTIN DREYLING, KENSEI TOBINAI, JULIE M.VOSE, JOSEPH M. CONNORS, MASSIMO FEDERICO, AND VOLKER DIEHL . *Revised Response Criteria for Malignant Lymphoma*. Journal of Clinical Oncology, 25(5):579–586, February 2007.

Bidimensionally measurable lesions with clearly defined margins by: 1) medical photograph (skin or oral lesion), or plain x–ray with at least 1 diameter .5 cm or greater (bone lesions are not included) or, 2) CT, MRI or other imaging scan with both diameters > the distance between cuts of the imaging study, or 3) palpation with both diameters ≥ 2 cm.

10.2.3 *EVALUABLE DISEASE:* unidemensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters < 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter < 2 cm, bone disease.

10.2.4 *NON–EVALUABLE DISEASES:* pleural effusions, ascites, disease documented by indirect evidence only (eg, lab values).

10.2.5 *OBJECTIVE STATUS, TO BE RECORDED AT EACH EVALUATION:* if an organ has too many measurable lesions to measure at each evaluation, choose 3 to be followed before patient is entered on study. Remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless *PD* is observed, objective status can only be determined when ALL is measurable and evaluable sites and lesions are assessed.

10.2.6 RESPONSE CRITERIA (RC)

Revised Response Criteria for Malignant Lymphoma Response Definitions for Clinical Trials (Cheson et al)				
Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variably FDG-avid or PET negative; regression to normal size on CT.	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a)FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT and PET b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed Disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy.	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

From "Revised Response Criteria for Malignant Lymphoma", B.D. Cheson, et. al. J Clin Oncol 25:579-586, 2007

10.2.7 END POINT DEFINITIONS

10.2.7.1 MAJOR END POINTS OF INTEREST

10.2.7.1.1 *RELAPSE:* return of signs and symptoms of cancer after a period of improvement.

Reappearance of any clinical evidence of lymphoma in a patient who has had a *CR*; relapse for *PR* is defined as *PD* relative to disease status during the *PR*; *Relapsed Disease* requires the following:

appearance of any new lesion or increase by ≥ 50% in the size of previously involved sites.

≥ 50% increase in greatest diameter of any previously identified node > 1 cm in its short axis or in the SPD of > 1 node.

10.2.7.1.2 *RELAPSE–FREE SURVIVAL (RFS):* Defined as the time from transplant to the first observation of relapsed disease or death due to any cause, whichever occurs first. If the patient has not relapsed or died, relapse-free survival is censored at the time of last follow-up.

10.2.7.1.3 *PROGRESSION–FREE SURVIVAL (PFS):* Time from transplant to disease progression or death from NHL.

10.2.7.1.4 *TRANSPLANT–RELATED DEATH (TRD)/TRANSPLANT–RELATED MORTALITY (TRM):* death that occurs during transplant admission; death due to causes unrelated to the underlying disease; death or mortality due to toxicities, adverse events or side effects occurring during or due to treatment; may be due to treatment procedures, drug toxicities, allergic reactions, and/or infections; patients relapsing are censored as surviving at the time of relapse.

10.2.7.1.5 *MEAN SURVIVAL TIME:* average time that patients in clinical study remain alive; time is measured beginning either at diagnosis or start of treatment.

10.2.7.1.6 *OVERALL SURVIVAL (OS)/SURVIVAL RATE (SR):* Defined as the time from transplant to death due to any cause. If a patient is alive, survival time is censored at the time of last follow-up.

10.2.7.1.7 *RESPONSE RATE (RR):* percentage of patients whose cancer shrinks or disappears after treatment.

10.2.7.2 SECONDARY END POINTS OF INTEREST

10.2.7.2.1 *DURATION OF RESPONSE/RESPONSE DURATION (DR):* interval from onset of response to *PD*; initial documentation of response until date of relapse or *PD*.

For patients with *PR*, measured from initial documentation of *PR* to time when cancer begins to enlarge or spread again.

10.2.7.2.2 *TIME–TO–[DISEASE]–PROGRESSION (TTP):* interval from first infusion to *PD*; entry onto trial until date of initial observation of *PD* or death due to any cause; measure of time after a disease is diagnosed (or treated) until the disease starts to get worse.

10.2.7.3 *PROGRESSION OF DISEASE/PROGRESSIVE DISEASE (PD):* cancer that continues to grow or spread, increasing in scope or severity; increase in the size of a tumor or spread of cancer in the body.

50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer); for *scan only* bone disease, increased uptake does not constitute clear worsening; worsening of existing non–evaluable disease not constitute *PD*.

10.2.7.3.1 *Lymphoma:* new sites of lymphadenopathy or increase of > 25% in lymph node size (as assessed by CT scans, blood or BM involvement with clonal B cells.

10.2.7.3.2 *CLL:* new sites of lymphadenopathy or increase of > 25% BM involvement or increase in > 25% blood involvement (if lymphocyte count > 50,000).

10.2.8 *RESPONSE ASSESSMENT:* response is currently assessed on the basis of clinical, radiologic, and pathologic (ie, BM) criteria.

10.2.8.1 CT scans remain the standard for evaluation of nodal disease; thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL; studies will be performed no later than two months after treatment has been completed to assess response; interval may vary with type of treatment, eg, a longer period may be more appropriate for biologic agents where the anticipated time–to–response may be greater.

10.2.8.2 A BM aspirate and Bx will only be performed to confirm a *CR* if they were initially positive or if it is clinically indicated by new abnormalities in the PB counts or blood smear.

10.3 PERFORMANCE STATUS Ω §§ B.001, C.001, D.003, I.001–I.003, J.001–J.003

ECOG (ZUBROD)/KARNOFSKY PERFORMANCE STATUS SCALES/SCORES *PERFORMANCE STATUS CRITERIA* Karnofsky performance scores are intended to be multiples of 10.			
ECOG (ZUBROD)		**KARNOFSKY**	
Score	Description	Score	Description
0	Fully active, able to carry on all pre–disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carryout work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or do active work.
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about > 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited Self care, confined to bed or chair > 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead		

11.0 INTERNAL REGULATORY REQUIREMENTS Ω §§ A.002, A.011, A.012, J.001–J.003

11.1 INSTITUTIONAL REVIEW BOARD (IRB) Ω §§ A.002, A.011, A.012, J.001–J.003

This protocol has been submitted to and approved by the *IRB* according to COHNMC ethical and regulatory guidelines.

11.2 CANCER PROTOCOL REVIEW AND MONITORING COMMITTEE (CPRMC) Ω §§ A.002, A.011, A.012, J.001–J.003

This protocol has been submitted to and approved by the *CPRMC* according to COHNMC ethical and regulatory guidelines.

11.3 DATA AND SAFETY MONITORING

A) Definition of Risk Level

This is a Risk Level 4 study, as defined in the “City of Hope Data and Safety Monitoring Plan”, http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx involving the use of RIT and chemotherapy as preparative conditioning for patients undergoing allogeneic hematopoietic stem cell transplantation for treatment of high-risk non-Hodgkin Lymphoma. Given that 1) the preparative regimen is considered novel and 2) if successful, the impact of this treatment on high-risk lymphoma may be great, this protocol has been classified as a Risk Level 4 study.

B) Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA/protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

Data and safety will be reported to the COH DSMC using the PMT report and submitted quarterly from the anniversary date of activation. Protocol specific data collection will include the following items: (on Teleform and MIDAS case report forms) patient-, donor-, disease-, treatment-characteristics, toxicity/complication data, and outcome data (e.g., disease status post transplant and vital status). From these data the PMT will monitor: 1) the patients' ability to tolerate the conditioning regimen, 2) complication/toxicity data watching for an excessive events including infections, delayed engraftment, and acute- chronic- GVHD, and 3) treatment related mortality events.

C) Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death
- Is life-threatening event (places the subject at immediate risk of death from the event as it occurred);
- Unplanned hospitalization equal or greater than 24 hours or prolongation of existing hospitalization

- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary Malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

D. Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/). After day 100 post transplant, expedited reporting of SAEs are only required for SAEs that are considered Unanticipated Problems, or second malignancies.

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		

	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

12.0 ETHICAL CONSIDERATIONS Ω §§ A.003–A.007

12.1 HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPPA) Ω §§ A.003–A.007

Protected Health Information (PHI) of those taking part in this protocol will not be made available to persons or entities not granted authority by a public health agency pursuant to the HIPPA of 1996 and the HIPPA Privacy Rule (Standards for Privacy of Individually Identifiable Health Information). COHNMC will not share PHI with others not authorized. PHI may be made available to the National Institutes of Health (NIH), Center for Disease Control (CDC), Health Resources and Services Administration (HRSA), Occupational Safety and Health Administration (OSHA), Substance Abuse and Mental Health Services Administration (SAMHSA), tribal health agencies, state public health agencies, local public health agencies, and/or entities granted authority by a public health agency. The Privacy Rule does permit disclosure of PHI for specified public health purposes.

12.2 MEASURES TO ASSURE PROTECTED HEALTH INFORMATION (PHI) CONFIDENTIALITY Ω §§ A.003–A.007

PHI in Patient Medical Records and Clinical Research Protocol Data is maintained in strictest confidence.

12.2.1 HEALTH INFORMATION MANAGEMENT SERVICES (HIMS)

HIMS controls and maintains all inpatient and outpatient medical records and the original documents within. All patients are assigned a Medical Record Number (MRN). Patient medical records are filed and requested by that MRN, not the patient's name.

12.2.2 DIVISION OF INFORMATION SCIENCES/DEPARTMENT OF CLINICAL RESEARCH INFORMATION MANAGEMENT

A CRA will be assigned to this protocol by the *Department of Clinical Research Information Management*. The CRA will be responsible for all protocol data collection and maintenance. The data collected on each patient will be captured on case report forms that are kept within a research file folder. Each patient's research file folder will be stored in a locked file room. Access is restricted to personnel authorized by the *Division of Information Science*s. Each patient's research file can be requested and accessed by protocol number and Research Participant Number (RPN), not the patient's name or MRN.

Should results from this protocol be reported in a medical journal or at a scientific meeting, PHI will be withheld. Any publications or presentations will refer to the patient by protocol number and RPN, not by name or medical record number.

13.0 FORMS AND DATA MANAGEMENT Ω §§ A.003–A.007, A.011, A.012, B.001, B.004, C.001

13.1 INFORMED CONSENT Ω §§ A.003–A.007, A.011, A.012, B.001, B.004, C.001

A conference will be held with each patient and family to discuss this protocol and alternative treatments. The PI will conduct the conference. The patient will each be provided the COHNMC IRB approved *Informed Consent for Participation in Research Activities* (ICF) and *Experimental Subject Bill of Rights.*

The consent as well as all potential risks associated with RIT, Chemotherapy, Immunosuppressive Drugs, AHSCT and DLI will be discussed and explained as objectively as possible. The procedure for collecting Peripheral Blood Mononuclear Cells (PBMCs) and the toxicities of G–CSF will be explained to the donor. The donor will be counseled as to the risks of treatment with G–CSF and will be informed that leukapheresis at several time points will be necessary. The Principal Investigator(s) will allow ample time for questions and answers if or as requested by the patient and/or sibling donor.

Upon agreeing to participate, each patient will sign and date the ICFs/Bill of Rights. Copies of these documents will be provided to each patient and sibling donor. The originals and copies of ICFs/Bill of Rights and any other appropriate assurances or agreements required will remain on site at COHNMC (originals in patient's/donor's medical records and copies in the *Department of Clinical Research Information Management*).

13.2 REGISTRATION GUIDELINES Ω §§ A.007, A.011, A.012, B.001, B.004, C.001

Registration will occur centrally at COHNMC. Each patient will be registered upon signing and dating the ICF/Bill of Rights and a medical evaluation to determine eligibility. To register a patient, the protocol nurse or CRA at COHNMC must complete the eligibility form and registration form to verify eligibility. The CRA will then assign a study number, a dose and register the patient onto the study.

13.3 PROCEDURES FOR WAIVERS OF ELIGIBILITY AND TREATMENT DEVIATIONS Ω §§ A.011, A.012

The PI must approve all *Waivers of Eligibility* prior to patient registration and all *Treatment Deviations* prior to treatment. The treating physician must contact the PI. Upon approval, the PI must submit a protocol amendment to the IRB.

13.4 DATA MANAGEMENT Ω §§ A.003–A.007, B.001

The *Department of Clinical Research Information Management* maintains a database to store and retrieve patient data collected from a wide variety of sources. The investigator will assure that data collected conform to all established guidelines for coding, collection, key–entry, and verification.

13.5 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE Ω §§ A.003–A.007, B.001

14.5.1 *CONFIDENTIALITY OF RECORDS:* Original data collection forms will be filed in secure cabinets in Biostatistics. All RIT associated data will be filed in RIT.

14.5.2 *PATIENT AND DONOR CONSENT FORMS:* At the time of registration, the signed and dated ICFs/Bill of Rights must be available for patient, donor, chart, and *Department of Clinical Research Information Management*.

14.0 Statistical Considerations

This phase II study is designed to demonstrate broad non-inferiority of RIT with conventional RIC treatment. This study is expected to accrue 46 patients. The primary endpoint will be relapse/progression

rate at two years. Based on a similar COH, FHCRC, and Stanford University cohort, the relapse rate at 2 years was estimated to be approximately 36%[27-31]. Assuming a non-inferiority null hypothesis with a 20% delta bound, a test with a one-sided type 1 error rate of 0.10 would have 80% power for rejecting the inferiority hypothesis if the long-run relapse rate was in fact 0.36. In addition, approximately 15 patients (of the required 46) will have samples collected pre- post-AHCT as part of costimulatory studies. Products from sibling donors will also be studied among this subset of patients. The expected number is 8, which is approximately 50-60%, which aligns with the expected rate of allo transplants that will utilize a sibling donor. The projected total study accrual, including primary study objective and secondary costimulatory studies, is 54 patients (46 patients + 8 donors).

Phase II Monitoring

Early stopping rules are incorporated into this trial for excessive toxicity however, there will be no interim analysis for efficacy. Toxicities will be recorded using two distinct grading systems; the modified Bearman Scale (Bearman, S., et al, JCO, Vol 6, No 10 (Oct), 1988, pp1562-1568. See appendix I for details.) and the NCI CTCAE 3.0 Scale. Generally, the modified Bearman Scale will be used to define (grade) 'early stopping' events (toxicities), and the NCI CTCAE 3.0 Scale will be used for reporting adverse events. The only exception relates to how hematologic toxicities are graded and incorporated into the early stopping criteria. For hematologic toxicities the CTCAE 3.0 Scale will be used. The table below will be consulted as relevant toxicities are encountered, so there will be no accrual-based interim analysis point.

Early Stopping Criteria: For each adverse outcome, stop if the cumulative number of patients reaches or exceeds the following limits:

Table of Early Stopping Criteria

# of patients treated	# of patients with grade 3 toxicities that would require an evaluation for safety per Bearman Scale*	# of patients with treatment related grade 4 or 5 toxicity that would stop the study**	Cumulative probability of early stopping given a DLT rate of:		
			1/6	22%	1/3
12	4	3	0.04	0.09	0.27
18	6	5	0.05	0.12	0.39
24	8	6	0.05	0.14	0.47
30	10	8	0.06	0.15	0.52
36	12	9	0.06	0.16	0.56
42	14	11	0.06	0.16	0.60

* Note: For hematologic toxicities: Any grade 4 neutropenia associated with fever or infection and lasting beyond three weeks, or grade 4 neutropenia lasting for more than 28 days per CTCAE 3.0 toxicity criteria should be counted toward the early stopping rule.

** Note: The stopping rules are not statistically based; expected treatment related mortality not to exceed 25%. Grade 4 for Bearman, Grade 5 for CTCAE 3.0.

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically according to the treatment schedule for the development of any toxicity. The toxicity rule for safety will be assessed as each patient reaches day +30 post transplantation. If more than the specified number of patients (noted in the table above) have significant treatment related toxicities, then the safety of the study will be evaluated.

Analysis of Clinical Endpoints

Toxicities observed will be summarized in terms of type (organ affected or laboratory determination), severity (by NCI CTC and nadir or maximum values for the laboratory measure) and time of onset. For grade 4 neutropenia, duration will be recorded. In accordance with the primary study objectives, we will perform descriptive statistical analyses on these data after the study is complete. Response rates and duration of response will be estimated. Confidence intervals for the response rate will be established by calculating the exact 95% confidence limits for a binomial parameter. Additional analyses will be

conducted to evaluate the post transplant toxicity/complication profile including acute and chronic GvHD and infectious complications.

Descriptive statistics will be used to characterize the expression of six costimulatory molecules (PD-1, CTLA-4, CD28, ICOS, OX40 and 4-1BB) pre- post- RIT based ASCT. Exploratory analyses will also be performed to assess the impact of these molecules on the NK and T cells of lymphoma patients pre- post- RIT based ASCT.

The product-limit method of Kaplan and Meier will be utilized to estimate time-to-event endpoints such as relapse/progression-free survival, overall survival, and non-relapse/progression mortality rate. We will consider univariate Cox models for the analysis of potential prognostic factors of time-to-event endpoints, including such factors as histologic grade, age at transplant, and disease stage as independent variables, first performing diagnostics to confirm the validity of the proportional hazards assumption. Descriptive comparisons with recent historical data from similar patient populations will be made to evaluate differences in relapse/progression-free survival, overall survival, relapse/progression rate, and toxicities.

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Appendix I

Modified Bearman Toxicity Scale

	Grade I	Grade II	Grade III
Cardiac Toxicity	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on chest x-ray with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestiveheart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder Toxicity	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal Toxicity	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary Toxicity	Dyspnea without chest x-ray changes not caused by infection or congestive heart failure; or chest x-ray showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	Chest x-ray with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO2 (> 10% from baseline) but not requiring mechanical ventilation or > 50% O2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF
Hepatic Toxicity	Mild hepatic dysfunction with bilirubin ≥ 2.0 mg/dL and ≤ 6.0 mg/dL or weight gain > 2.5% and < 5% from baseline, of non-cardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin > 6.0 mg/dL and < 20 mg/dL; or SGOT increase > 5-fold from preconditioning; or clinical ascites or image documented ascites > 100 mL; or weight gain > 5% from baseline of non-cardiac origin	Severe hepatic dysfunction with bilirubin > 20 mg/dL; or hepatic encephalopathy; or ascitis compromising respiratory function
CNS Toxicity	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI Toxicity	Watery stools > 500 mL but < 2,000 mL every day not related to infection	Watery stools > 2,000 mL every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

NOTE: Grade IV regimen-related toxicity is defined as fatal toxicity.