MSK PROTOCOL COVER SHEET

An Intention-to-Treat Study of Salvage Chemotherapy Followed by Allogeneic Hematopoietic Stem Cell Transplant for the Treatment of High-Risk or Relapsed Hodgkin Lymphoma

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1.0 PROTOCOL SUMMARY AND SCHEMA

This is a phase 2 intention-to-treat study of salvage chemotherapy followed by allogeneic hematopoietic stem cell transplant (HSCT) for the treatment of primary-refractory or relapsed Hodgkin Lymphoma (HL). The primary aim is to obtain a preliminary estimate of the progression-free survival at 1 year post-transplant.

Patients aged 13-65 years with primary-refractory or relapsed HL who are suitable allograft candidates will be enrolled on the intention-to-treat study prior to salvage chemotherapy. This will include patients who fail primary therapy and have all 3 risk factors (B-symptoms; extranodal sites of disease; disease remission < one year after first-line therapy), or those who have 2 risk factors and remain PET+ after salvage chemotherapy, or those with primary progressive disease, or those who have failed platinum-based chemotherapy. In addition, patients who relapse no earlier than 100 days after an autologous stem cell transplant will also be included.

Eligible patients will receive 2-3 cycles of second-line combination chemotherapy, using standard regimens. Alternatively, patients may also be treated on ongoing MSKCC phase I or II studies specific for Hodgkin Lymphoma.

Patients who 1) do not progress on salvage chemotherapy, and 2) have both suitable HSC donors and 3) a satisfactory pre-allograft work-up will proceed to allograft. Patients who fail any of these 3 criteria will be off-study and considered treatment failures for the purposes of the intention–to-treat study.

Patients referred with responsive or stable disease after receiving salvage chemotherapy or who require more than one second-line combination chemotherapy regimen, will not be included in the intention-to-treat analysis of the study but can proceed to allograft on protocol if they are suitable candidates. While they will contribute to the allograft outcome data, they will not be part of the primary efficacy analysis described below. It is anticipated that approximately 6 patients will be treated through this course.

Pre-allograft conditioning and post-graft immune suppression will be determined by remission status post salvage chemotherapy assessed at the time of pre-allograft work-up.

- Patients who have stable disease or are in PR will receive a reduced intensity preparative regimen of Melphalan and Fludarabine (Mel/Flu).
- Patients in CR will receive a non-myeloablative preparative regimen of Cyclophosphamide, Fludarabine and low dose total body irradiation (Cy/Flu/TBI).

Hodgkin's relapse or disease progression will be defined using CT and PET criteria. Complete remission is defined as resolution of all disease related symptoms and normalization of PET scan and of bone marrow involvement on morphologic exam. Partial remission (PR) is ≥ 50% decrease in the sum of product of diameters (SPD) of the 6 largest dominant lymph nodes and of sites of organ involvement, no increase in size or number of involved lymph nodes or organs, decrease in PET avidity. Stable disease (SD) is less than PR but is not progressive disease. Progressive/ relapsed disease (PD) is appearance of a new lesion ≥50% increase in SPD of more than one node or in greatest diameter of any previously identified node >1 cm in its short axis.

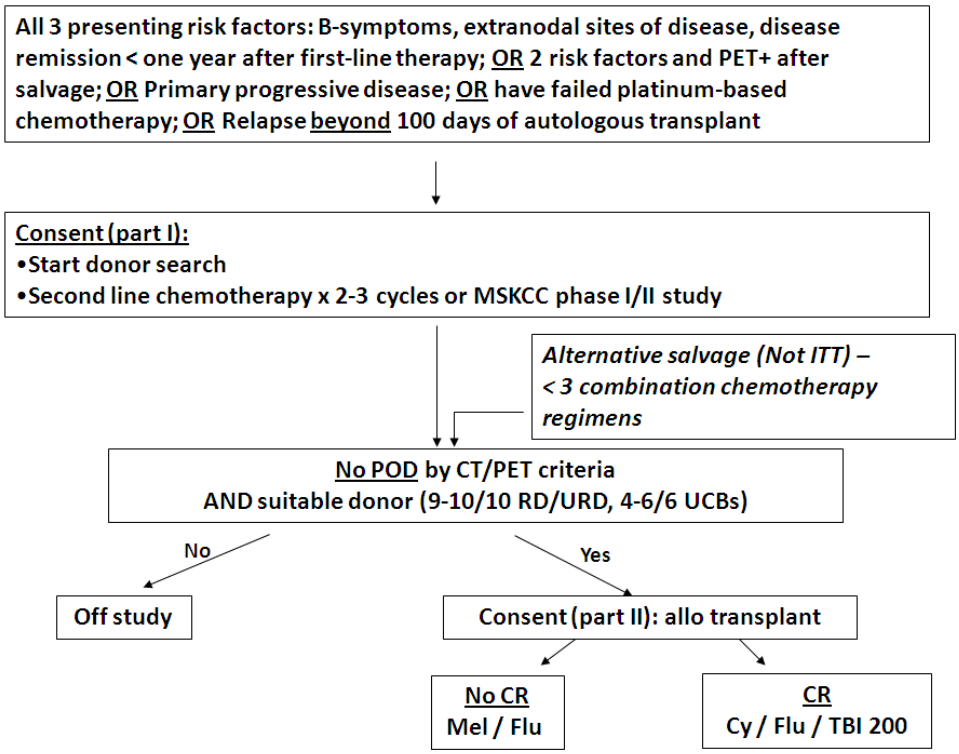
Cytoreduction will be followed by transplantation using the best available donor according to the BMT Service donor algorithm (sibling or unrelated donor (URD) peripheral blood stem cells (PBSC), or bone marrow (BM), or umbilical cord blood (UCB)). Immune suppression will be with Tacrolimus, Sirolimus and Methotrexate for related or unrelated donors, and cyclosporine-A (CSA) and mycophenolate mofetil (MMF) for UCB. In the absence of GVHD, withdrawal of immune suppression in patients who proceed to allograft with less than a PR will be done more rapidly than in patients in PR or CR (off by 120 days instead of 6 months). Patients with progression of disease (POD) prior to allograft will not undergo allo-HSCT.

Patients will be carefully monitored for toxicity from the salvage chemotherapy, and post-allograft for donor engraftment and count recovery, donor chimerism, the incidence and severity of acute and chronic graft-versus-host disease (GVHD), transplant-related mortality (TRM), characteristics of immune recovery, as well as overall and progression-free survival.

Biostatistics will be based on a sample size of 30 patients (24 on ITT study, and 6 transplanted without salvage therapy administered on protocol) and it is anticipated that approximately 24 of these patients will proceed to allograft. The accrual period will be approximately 4-5 years with a follow-up period of 2 years post-transplant.

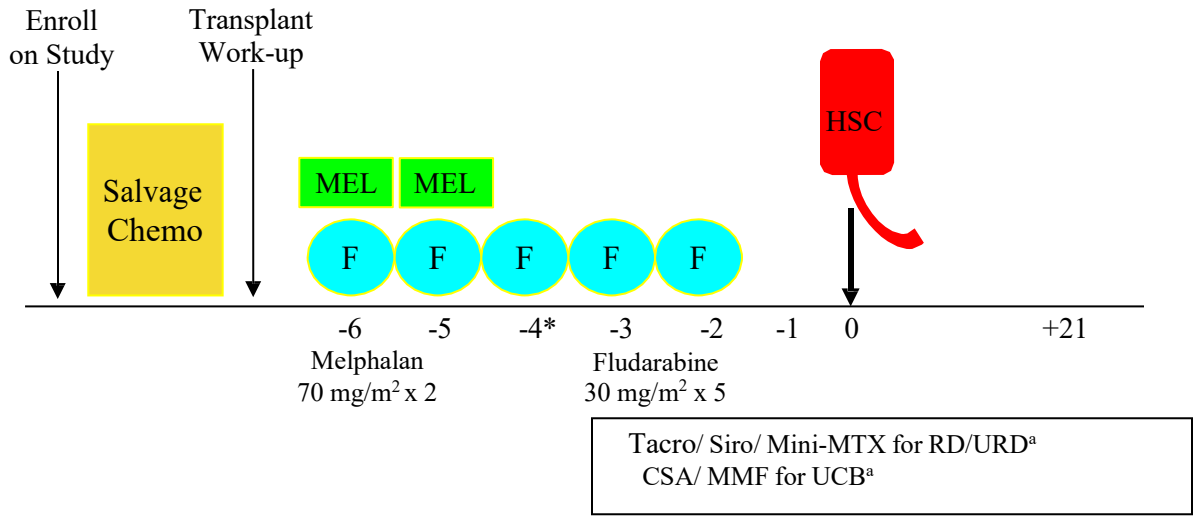
For this study, a patient will be classified as a success, if he or she responds due to salvage chemotherapy, undergoes an allogeneic HSCT, and remains progression free for one year after HSCT. Currently, 5 of 15 patients are recorded a success on this study. These 15 patients are incorporated into a Simon two-stage minimax design that differentiates between success rates of 0.20 and 0.45. In the first stage, since more than 3 successes out of 15 patients were observed, an additional 9 patients will be accrued for a total of 24 patients. The salvage chemotherapy followed by HSCT would be considered worthy of further study in this patient population if 8 or more successes from the 24 patients were observed. This two-stage design has power 0.90 if the population success proportion is 0.45 and has a type 1 error equal to 0.10 at the success probability 0.20.

1.1 PROTOCOL SCHEMA



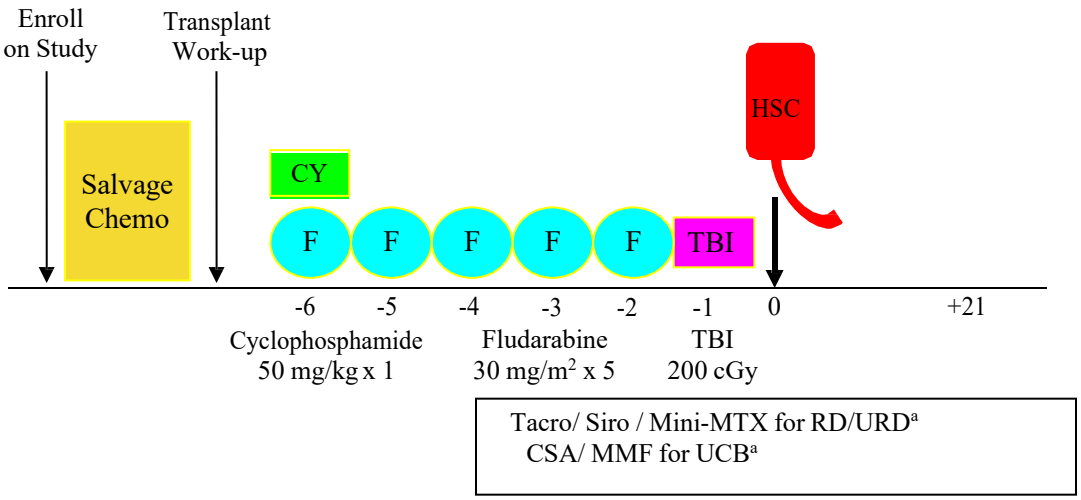
1.2 ALLOGRAFT TREATMENT PLAN

Reduced Intensity Conditioning for Patients in SD or PR



[a] *withdrawal of GVHD prophylaxis determined by response to salvage therapy.*

Non-Myeloablative Conditioning for Patients in CR



[a] *withdrawal of GVHD prophylaxis determined by response to salvage therapy.*

Abbreviations: *MEL: melphalan; FL: fludarabine; CY: cyclophosphamide; TBI: total body irradiation; HSC: hematopoietic stem cells; MTX: methotrexate; CSA: cyclosporine; MMF: mycophenolate mofetil; Tacro: Tacrolimus; Siro: Sirolimus; RD: related donor; URD: unrelated donor; UCB: umbilical cord blood*

2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.2 Primary Objectives

Patients with Hodgkin Lymphoma (HL) relapsed post-autograft are not able to be cured with standard chemotherapy regimens. In addition, a subset of relapsed and primary-refractory patients with HL fare poorly with conventional autologous transplant. Such patients may benefit from allogeneic transplantation secondary to a graft-versus-malignancy (GVM) effect[1-7]. This protocol investigates an intention-to-treat approach to such patients with salvage chemotherapy followed by allogeneic hematopoietic stem cell transplant (HSCT) for the treatment of high-risk or relapsed HL.

The primary aim of this study is to obtain a preliminary estimate of the progression-free survival at 1 year after allo-HSCT.

2.3 Secondary Objectives

2.2.1 Transplant Outcome

- the speed of neutrophil and platelet recovery post allograft
- the incidence and speed of donor-derived engraftment post allograft
- the incidence and severity of acute GVHD at 100 days post allograft
- the incidence and severity of chronic GVHD at 1 year post allograft
- the incidence of TRM at 100 and 180 days post allograft

2.2.2 Overall and Disease Outcome

- the incidence of relapse or disease progression at 1 and 2 years post allograft
- the probabilities of overall survival at 1 and 2 years post allograft

- the probabilities of progression-free survival at 2 years post allograft

2.2.3 Intention-to-treat Analysis

- the number of patients enrolled on the intention to treat study proceeding to allograft
- the probabilities of overall and progression-free survival at 1 and 2 years for all patients on the intention-to-treat study

2.2.4 Biology of UCB transplant

- the performance of laboratory studies investigating double unit biology and their correlation with unit engraftment in the patient.

3.1 BACKGROUND AND RATIONALE

3.2 Introduction

The majority of patients with HL are cured with standard chemoradiotherapy approaches. However, patients who relapse after attaining a complete remission with chemotherapy and those with primary refractory disease have a poor outcome with conventional-dose salvage regimens. Over the past 15 years, several clinical trials using high dose chemotherapy or chemoradiotherapy with autologous stem cell transplantation (ASCT) in this setting have been reported, and approximately 40% of patients appear to be cured using this approach.[8] Two randomized studies comparing standard-dose second-line chemotherapy with high dose therapy (HDT) and ASCT have been reported.[9,10] Each study demonstrated a statistically significant improvement in both event-free and progression free survival for the patients treated on the HDT arms, but neither was powered to show an overall survival advantage. Despite the success with HDT/ASCT, more than 50% of patients fail this approach; median survival of these patients is 15 months.

3.3 Chemosensitive disease is required to achieve benefit from HDT/ASCT

The importance of pre-transplant cytoreduction with salvage therapy (ST) has been demonstrated in numerous series. In 1991, we reported our results using high dose combined modality therapy in patients with biopsy-confirmed relapsed and primary refractory HL in our first generation programs (MSKCC protocols 85-97 and 86-86). The program utilized accelerated fractionation radiotherapy either as total lymphoid irradiation (TLI) or as an involved field (IFRT) followed by high dose chemotherapy and bone marrow infusion. One hundred and fifty-six patients were treated; chemosensitive disease was not a requirement for transplantation however patients were given non-uniform second-line standard dose chemotherapy with the hope of debulking disease pre-ASCT. At a median follow-up of 11 years the EFS is 45% with no relapses occurring later than 36 months post-ASCT. After the introduction of G-CSF, 100 day mortality decreased form 18% to 6%.[11,12] These results demonstrated the feasibility of incorporating dose intensive radiotherapy into HDT for HL and most importantly the study determined that patients with chemosensitive disease to ST pre-HDT/ASCT have a marked improvement in EFS compared to patients with refractory disease at the time of HDT. As with aggressive non-Hodgkin's lymphoma, chemosensitive disease to ST is now required for transplant eligibility in the United States.

3.4 ICE chemotherapy is a highly effective standard-dose second-line regimen in HL

In 2001 we reported the results of a comprehensive program for 82 patients with relapsed and refractory HL (MSKCC 94-68/97-51).[13] All patients received uniform cytoreduction with ifosfamide, carboplatin and etoposide (ICE) and only responders were subsequently offered HDT and ASCT. All patients in this trial had biopsy-proven relapsed or refractory disease, and our data were analyzed by intent-to-treat. The Kaplan-Meier estimate of the proportion of patients who are alive, event-free and analyzed by an intent-to-treat at a median follow-up for surviving patients of six years is 55%. In the subset of patients who received HDT/ASCT (75 of 82 patients), the EFS is 61%. The response rate to ICE was 85% and only 12% of patients had an inadequate peripheral blood progenitor cell (PBPC) harvest. In addition, integrating higher dose chemotherapy into the transplant conditioning regimen was safe; with a 100 day mortality of 2.6%. These results compare very favorably with reports in the literature. Our program documents the feasibility and efficacy of: (1) ICE chemotherapy as a highly effective dose dense/intense cytoreductive regimen in HL and (2) integrating higher dose radiotherapy into an ASCT treatment program.

3.5 A three-factor model predicts outcome in relapsed and primary refractory HL

Response to second-line chemotherapy has been used as the major selection criteria to proceed to ASCT, but other prognostic factors may also predict for long-term EFS in patients with relapsed and refractory HL. In MSKCC protocol 94-68, Cox regression analysis determined that the factors associated with a poor outcome pre-ICE chemotherapy were: extranodal sites of disease (ENS), $p < 0.001$, initial response duration < 1 year ($p = 0.001$), and B symptoms ($p < 0.001$). Using this 3 factor model we identified 3 groups of patients with widely disparate outcome with this treatment approach. The largest group, 65% of the total number of patients had 0-1 of these risk factors. This favorable group had an EFS of 80% measured from initiation of ICE therapy. Patients with 2 and 3 risk factors fared less well with an EFS of 34% and 12% respectively.

3.6 Risk-Adapted therapy

Risk-adapted therapy can improve EFS in patients with relapsed and refractory HL. This 3 factor model was the basis of our recent risk-adapted comprehensive study (MSKCC protocol 98-71). The expectation from risk-adapted therapy is a reduction in the influence of risk factor (RF) on outcome by improving the results of patients in the less favorable groups. Our strategy was to intensify therapy without increasing toxicity for unfavorable patients with multiple risk factors, while at the same time, maintaining the previous regimen used successfully for the favorable cohort. The primary endpoint of this study was to improve outcome by diminishing the significance of the three factor prognostic model with tailored therapy. In this study of 105 patients, the median follow-up of the patients is now 4.5 years and patients with multiple RF have an improved EFS as compared to our previous results. Patients with 0 or 1 risk factor (ENS, initial response duration < 1 year or B symptoms at time of study enrollment), group A, were treated exactly as those on the 1994 -1998 program. The outcomes of the favorable patients between the two studies is similar, hence we prospectively confirmed the results in good risk patients. Patients with 2 RF have a 3-year EFS of 46% (95% CI: 31%-62%); the 3-year EFS from the previous study was 27%. The 3-year EFS for patients with 3 factors is 46% (95% CI: 20%-71%); the 3-year EFS was 10% in our previous study. This improved EFS in patients with 3 RF was obtained after tandem ASCT, an approach that is considered investigational at the present time.

Despite an 85% response rate to ST, 35% of patients with 0-2 RF will die of their disease. The incorporation of non-cross resistant chemotherapy regimens that include gemcitabine and IMRT to further cytoreduce disease burden prior to HDT, in an attempt to improve EFS, is reasonable and is the basis of our current study MSKCC protocol 04-047, which excludes patients with all 3 risk factors.

3.7 Abnormal Functional imaging pre-ASCT predicts a poorer outcome in patients with chemosensitive disease

Our prognostic model is based upon pretreatment factors; however, since almost all patients have cytoreduction to "ICE" chemotherapy, other factors, evaluated at the time of HDT, may be important. Reports by other groups have shown that tumor bulk of < 5 cm or being in a complete response pre-ASCT portended an improved survival. We evaluated both of these factors in our 2 studies (94-68 and 98-71) and they did not predict outcome. Patients with HL commonly have large residual masses secondary to underlying sclerosis of the tumor and only a minority of patients achieves a true CR pre-ASCT. However all of our patients have functional imaging, PET or gallium scanning, pre and post ICE and we evaluated the effect of normalization of functional imaging pre-ASCT on outcome. There was a marked survival advantage for patients who normalize their functional imaging (FI) pre-ASCT. For all transplanted patients the EFS is 64.3% however the patients with normal FI have an EFS of 76% vs 40% for patients with abnormal imaging ($p < 0.0001$). This was most important for patients with favorable risk factors, ARM A, where the EFS is 85% for patients with normal FI vs 25 % for patients with abnormal FI, $p < 0.0001$. Despite the more dose intense regimens used in patients with 2 or 3 risk factors in protocol 98-71, patients with abnormal functional imaging pre-ASCT had a very poor outcome.

3.8 Gemcitabine-based therapy in HL

Treatment for HL patients who fail ASCT is palliative with no standard. We retrospectively evaluated our experience with two active agents, gemcitabine (G) and vinorelbine (N, Navelbine), given in combination for patients who fail ASCT. Thirteen patients received GN, median age 33 (range 23-46). Patients had progressed following ASCT (median 7.4 months; range 2.9-51) and had received 3-7+ prior cytotoxic regimens. The median number of treatments for responding patients was 11 (range 5-47); median follow-up for surviving patients is 17.5 months. 9/13 patients (69%) responded or had stable disease. The median freedom-from-progression (FFP) and OS for all patients was 7.4 months (95% CI 0.7, 14.1) and 30.4 months (95% CI 5.5, 55). Gemcitabine (G), vinorelbine (N, Navelbine), and liposomal doxorubicin (D) have been studied by the CALGB Between 7/15/00 and 12/9/02. Seventy-six patients with recurrent or refractory HL were accrued to this CALGB Phase I/II trial of GND. The objectives were to determine the maximal tolerated dose (MTD), response rates, and toxicity of this combination. All patients had measurable disease, no prior treatment with these agents, ANC > 1500 and platelets >100,000. Any number of prior therapies was allowed. 28 patients had prior ASCT. Results: The Phase I portion of the study identified G 1000 mg/m2 d1, 8, N 20 mg/m2 D1, 8, and D 15 mg/m2 D1, 8 Q21 days as the MTD. Febrile neutropenia and mucositis were the dose-limiting toxicities. A planned interim analysis of the Phase II portion of the study showed overall response rates of 58% (95% exact CI [0.34, 0.80]) for the first 19 patients without prior transplant (8 PR, 3 CR) and 68% (95% exact CI [0.44, 0.87]) for the 19 patients with prior transplant (12 PR, 1 CR). Complete toxicity data is available for 23

of the 38 interim analysis patients. The regimen was well tolerated. Grade 3-4 toxicities included neutropenia (69%), thrombocytopenia (17%), febrile neutropenia (9%), mucositis (9%), and pulmonary (17%). There were no treatment related deaths. They concluded that GND is an active, well-tolerated, non-alkylator based regimen that should be considered both in the pre-transplant salvage setting as well as for patients relapsing after transplant.

Gemcitabine has also been combined with ifosfamide and vinorelbine (IGV) in patients with relapsed/refractory HL.[14,15] This regimen has been well-tolerated and has been used pre-ASCT. In a recent report, 32 patients were treated with salvage chemotherapy (IGEV, ifosfamide, gemcitabine, and vinorelbine), followed by a tandem ASCT (melphalan 200 mg/m^2, BEAM). In an intention-to-treat analysis, the overall response rate increased after each stage of protocol, ranging from 47% to 65% and 75% after IGEV, MEL200, and BEAM, respectively.[14]

3.9 Clinical Results of Allotransplant in HL

An alternative treatment strategy for poor risk patients (pts with all 3 risk factors) would require investigators not to offer HDT and ASCT to this subgroup but instead, a non-myeloablative allogeneic transplantation after some cytoreduction with ST. Recent evidence from several groups suggests that here is evidence of a graft vs. HL effect after non-myeloablative allogeneic transplantation[1].

3.9.1 Clinical Results with Sibling and Unrelated Donor HSCT

Initial studies of allo-HSCT demonstrated high TRM and low OS, likely due to the use of myeloablative regimens in heavily pre-treated patients.[16-20] More recent studies in which patients underwent reduced-intensity or non-ablative cytoreduction have shown improved outcomes and decreased TRM.[21-24] Peggs *et al.*[21] recently reported the results of reduced-intensity transplantation in 49 patients with multiply relapsed Hodgkin's lymphoma, 90% of whom had progression of disease after previous ASCT. Non-relapse-related mortality was 16.3% at 730 days (7.2% for patients who had related donors vs 34.1% for those with unrelated donors, p=0.0206). Projected 4 year overall and progression-free survival were 55.7% and 39.0%, respectively (62.0% and 41.5% for related donors). Eight of 49 (16%) had grade II-IV acute GVHD and seven (14%) had chronic GVHD before donor-lymphocyte infusion. Sixteen patients received donor-lymphocyte infusion from 3 months after transplantation for residual disease or progression and 9 showed disease responses after infusion (CR=8, PR=1). The patients enrolled on this clinical trial did not receive a true non-ablative regimen, but instead, a reduced intensity conditioning regimen that included 140 mg/m2 of melphalan. There is little doubt that this dose of melphalan is active in the treatment of HL. Investigators from MD Anderson have reported similar results with this approach.[23]

3.9.2 Clinical Results of Non-myeloablative UCBT: Overall and in HL

Results of unrelated donor UCBT have demonstrated that banked UCB is rapidly available[25] and can successfully engraft the majority of small children with a relatively low incidence of acute and chronic GVHD despite HLA disparity.[26] However, adult UCBT is limited by the low infused cell dose.[26-28] Therefore, for larger adolescents and adult patients undergoing UCBT, efforts must be

focused on improving engraftment and decreasing TRM. To address this problem the University of Minnesota has investigated the novel approach of the combined transplantation of two UCB units in a double unit graft after myeloablative conditioning as a strategy to augment graft cell dose.[29] These studies have shown that double unit UCBT can be performed safely in adults with improved engraftment and reduced TRM as compared to historical single unit controls. This strategy therefore extends access to allogeneic transplantation and introduces adult UCBT as a viable alternative to both matched and mismatched marrow transplantation. Further, given the relatively small cell dose of the engrafting unit, these results raise intriguing questions concerning the transplant biology of this approach. Therefore, further investigation of double unit UCBT is warranted.

The University of Minnesota has also investigated non-myeloablative UCBT, utilizing double unit grafts in those without satisfactory single units, to augment graft cell dose, in 59 high-risk adults (median age 49 years) with high-risk or advanced hematologic malignancies.[30]. Patients received cyclophosphamide 50 mg/kg, fludarabine 200 mg/m^2, and 200 cGy TBI ($\pm$ anti-thymocyte globulin), with cyclosporine-A and mycophenolate mofetil, and either single (n = 14) or double (n = 45) 4-6/6 HLA-matched UCB units with a median total infused dose of 3.4 x 10^7 NC/kg. Neutrophil recovery occurred at a median of 8 days (range 5-32). The cumulative incidence of sustained donor engraftment was 89% (95%CI: 81-97) overall, and 98% (95%CI: 94-100) in patients with a prior autograft or combination chemotherapy within the prior 3 months. The cumulative incidence of grade II-IV acute GVHD was 63% (95%CI: 49-77) at day 100, and chronic GVHD was 28% (95%CI: 16-40) at 1 year, with a TRM of 19% (95%CI: 9-29) at day 180. Notably, TRM was 14% in patients $\geq$ 45 years, 24% in patients with extensive prior therapy, and 44% in patients with significant co-morbidities. Cox regression analysis revealed that the relative risk of TRM by day 180 was 0.8 (0.2-3.2; p = 0.78), 1.5 (0.4-5.6; p = 0.56) and 8.0 (2.0-32.0; p < 0.01) in these 3 patient groups, respectively. With a median follow-up of 16 months (range 4-30), the probability of overall and progression-free survival was 44% (95%CI: 30-58) and 35% (95%CI: 21-49) at 2 years. Therefore, non-myeloablative UCBT is associated with prompt neutrophil recovery, a high incidence of sustained engraftment and relatively low TRM in older or extensively pre-treated adults provided they have satisfactory fitness and reasonable progression-free survival in this high-risk patient population.

The same group also recently reported on their experience in 9 patients with HL.[31] All patients sustained donor engraftment by day 60. Cumulative incidence of acute and chronic GVHD were 33% and 11%, respectively. TRM at 100 days was 11% and the 2 year PFS was 25% (95%CI: 0-55%). This approach will be investigated specifically in the treatment of HL in this protocol.

3.10 Summary

Although initial studies of allogeneic transplantation with myeloablative conditioning regimens were associated with poor outcomes due to high TRM in patients with HL, more recent studies with reduced intensity regimens have shown promising results. A number of lessons can be learned from our prior experience in the treatment of patients with relapsed and primary refractory HL:

1) 50% of these patients can be cured with HDT/ASCT;
2) Chemosensitive disease is required to achieve benefit from HDT/ASCT;

3) A 3 factor model that includes extranodal sites of disease (ENS), initial response duration < 1 year, and B symptoms predicts outcome in relapsed and primary refractory HL treated with HDT/ASCT;
4) Risk-adapted therapy can improve EFS in patients with relapsed and refractory HL;
5) PET scanning should be used to determine response and eligibility for transplant;
6) Recent evidence from several groups suggests that there is evidence of a graft vs. HL effect after non-myeloablative allogeneic transplantation.

Several important questions remain to be answered, including patient selection for ASCT vs. Allo-HSCT based on risk factors, timing of allo-HSCT, as well as the intensity of the conditioning regimen. Finally, most allo-HSCT studies report data of the transplant alone, but do not report the percentage of patients are actually able to undergo allo-HSCT for advanced lymphoma or leukemia. The goal of this protocol is to address these important questions.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a phase 2 intention-to-treat study of salvage chemotherapy followed by allogeneic HSC transplant for the treatment of primary refractory or relapsed HL. The primary aim is to obtain a preliminary estimate of the progression-free survival at 1 year post-transplant.

Patients aged 13-65 years with primary-refractory or relapsed HL who are suitable allograft candidates will be enrolled on the intention-to-treat study prior to salvage chemotherapy. This will include patients who fail primary therapy and have all 3 risk factors (B-symptoms; extranodal sites of disease; disease remission < one year after first-line therapy), or have 2 risk factors and remain PET+ after salvage chemotherapy, or those with primary progressive disease, or those who have failed platinum-based chemotherapy. In addition, patients who relapse no earlier than 100 days after an autologous stem cell transplant will also be included.

Patients referred with responsive or stable disease after receiving salvage chemotherapy or who require more than one second-line chemotherapy regimen, will not be included in the intention-to-treat analysis of the study but can proceed to allograft on protocol if they are suitable candidates. While they will contribute to the allograft outcome data, they will not be part of the primary efficacy analysis described below.

4.3 Intervention

Eligible patients will receive 2-3 cycles of second-line combination chemotherapy, using standard regimens. Alternatively, patients may also be treated on ongoing MSKCC phase I or II studies specific for Hodgkin Lymphoma.

Pre-allograft conditioning and post-graft immune suppression will be determined by remission status post salvage chemotherapy assessed at the time of pre-allograft work-up.

Patients who have stable disease or are in PR will receive a reduced intensity preparative regimen of Melphalan and Fludarabine (Mel/Flu).

Patients in CR will receive a non-myeloablative preparative regimen of Cyclophosphamide, Fludarabine and low dose total body irradiation (Cy/Flu/TBI).

Cytoreduction will be followed by transplantation using the best available donor (sibling or unrelated donor (URD) peripheral blood stem cells (PBSC), or bone marrow (BM), or umbilical cord blood (UCB)). Immune suppression will be with Tacrolimus, Sirolimus and Methotrexate for related or unrelated donors, and cyclosporine-A (CSA) and mycophenolate mofetil (MMF) for UCB. In the absence of GVHD, withdrawal of immune suppression in patients who proceed to allograft with less than a PR will be done more rapidly than in patients in PR or CR. Patients with progression of disease (POD) prior to allograft will not undergo allo-HSCT.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Melphalan (Alkeran®)

Supplied as: Powder for injection - 50mg single use vial with 10ml vial of sterile diluent.
Reconstitution directions: Reconstitute powder for injection with 10ml of supplied diluent and shake vigorously until a clear solution is obtained; provides a 5mg/ml solution.
Storage and Stability:

1. The Intact packages should be stored at room temperature (15-30°C).
2. Protect from light.
3. Shelf-life surveillance of the intact dosage form is ongoing.
4. Constitution with the special diluent as directed results in a solution that retains at least 90% potency for about three hours at 30°C.
5. Do not refrigerate the reconstituted product; a precipitate forms if the reconstituted product is stored $\leq$ 5°C.
6. Reconstituted solutions must be further diluted immediately, discard unused portion.
7. Drug administration must be completed within 60 minutes of initial reconstitution.

Preparation:

1. Upon reconstitution with supplied diluent, shake vigorously until the solution is clear.
2. Immediately dilute the dose to be administered in 0.9% Sodium Chloride, USP, to a concentration $\leq$ 0.45mg/ml.

Usual Dosage and Administration:

1. Consider dose reduction in patients with renal dysfunction based on creatinine clearance.
2. Do not administer IV Push.
3. Infuse diluted product over a minimum of 15 minutes via a Secondary Administration set.

Clinical Considerations: *Complete administration within 60 minutes of reconstitution.* The time between reconstitution and administration should be kept to a minimum because reconstituted and diluted solutions of Melphalan are unstable. Isolated case reports of skin ulceration and skin necrosis at the IV site of administration have been reported. Instruct patient in mouth care with sodium bicarbonate rinses (0.75ml of sodium bicarbonate in 1 liter of water) after meals and bedtime.

1. Hydration: Dependent on dosage.
2. Emetic potential: Moderate
3. Supportive medications: For doses > 100mg/m^2 give Furosemide (Lasix) 20mg IV x 1 Pre Med; initiate Hypersensitivity Order Set for signs and symptoms of hypersensitivity.

Toxicities: See Section 11.0
Incompatibilities: Complete data not available; do not administer with other drugs. Known contraindicative interactions with Cyclosporine, Buthionine Sulfoximine, Nalidixic Acid, and a variety of vaccines.

5.3 Fludarabine phosphate (Fludara®)

Supplied as: 50mg vial
Reconstitution Directions: add 2ml of sterile water for injection to a 50mg vial; yields a final concentration of 25 mg/ml.
Storage and Stability:
1. Store vials under refrigeration.
2. Refrigerated: prepare infusion in D5W; stable for 16 days.
3. Room temperature: prepare infusion in D5W; stable for 16 days.

Preparation:
1. Standard IV fluid: D5W.
2. Final infusion concentration range: up to 10mg/ml.
3. IV piggyback volume: 50 cc.

Clinical Considerations:
1. Hydration: 500 cc saline. May require higher fluid rate if at risk for tumor lysis.
2. Emetic potential: low.
3. Supportive medications: none.

Toxicities: see Section 11.0.
Incompatibilities: acyclovir, amphotericin B, chlorpromazine, daunorubicin, ganciclovir, hydroxyzine, miconazole, prochlorperazine.

5.4 Cyclophosphamide (Cytoxan®, Neosar®)

Supplied as: 200 mg, 500 mg, 2000 mg vials
Reconstitution Directions: add sterile water for injection to yield a final concentration of 20 mg/ml.
Storage and Stability:
1. Store vials at room temperature.
2. Refrigerated: prepare infusion in D5W, stable for 28 days.
3. Room temperature: prepare infusion in D5W: stable for 48 hours

Preparation:
1. Standard IV fluid: D5W.
2. Final infusion concentration range: 20mg/ml.
3. IV piggyback volume: for doses < 1200mg/m2, infuse in 25cc D5W; for doses> 1200mg, infuse as straight drug.

Clinical Considerations: hemorrhagic cystitis is a common side-effect but can be reduced by administering drug early in the day, high volume fluids, and encouraging patient to empty their bladder frequently. Drug may cause nasal congestion which can be improved by slowing the infusion. Must monitor electrolytes for SIADH.
1. Hydration: as per MSKCC guidelines.
2. Emetic potential: high and delayed.
3. Supportive medications: anti-emetics as per MSKCC guidelines .

Toxicities: see Section 11.0.
Incompatibilities: do not administer with other drugs.

5.5 Total Body Irradiation (TBI)

Treatment planning begins with a simulation. Patients will receive a total dose of 200 cGy on one day as a single fraction. Patients receiving total body irradiation (TBI) are treated in a standing position, and the treatment takes about 20 to 30 minutes. Toxicities are outlined in Section 11.0.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

6.1.1 Inclusion Criteria for Salvage Chemotherapy

- Histologic diagnosis of Classical HL, including those that are CD20+. Lymphocyte predominant histology will be excluded.
- Primary refractory or relapsed disease in patients with all 3 RF, or relapsed disease in patients with 2 risk factors who remain PET+ after salvage chemotherapy, or having failed platinum-based chemotherapy, or relapse beyond 100 days of autologous transplant, proven by biopsy or fine needle aspiration (cytology) of an involved site
- Failure of doxorubicin or nitrogen mustard containing front-line therapy
- 18F-fluorodeoxyglucose-PET scan demonstrating PET avid disease
- Cardiac ejection fraction of greater than 50% (patients > 18) or fractional shortening by echocardiogram greater than 50% (patients < 18), measured since last chemotherapy.
- Adjusted diffusing capacity of greater than 50% on pulmonary function testing, measured since last chemotherapy.
- Serum creatinine <1.5 mg/dl; if creatinine >1.5 mg/dl then the measured 12- or 24-hour creatinine clearance must be >60 ml/minute.
- ANC>1000/µl and Platelets>50,000/µl
- Total bilirubin < 2.0 mg/dl in the absence of a history of Gilbert's disease.
- Females of childbearing age must be on an acceptable form of birth control.
- Age between 13 and 65
- HIV I and II negative.
- Patients or their guardians must be capable of providing informed consent.

6.1.2 Inclusion Criteria for Allogeneic Transplant

Age and Donor Status:

- Patients aged 13-65 years at initial referral with a suitably matched donor.

Diagnosis:

- Patients with HL without progression of disease (POD) after salvage chemotherapy.

Pre-allograft Salvage Chemotherapy:
This can include standard chemotherapy regimens (e.g. Ifosfamide/ Gemcitabine/ Vinorelbine, MOPP, or another regimen) ≥ 2 cycles, OR participation in ongoing MSKCC phase I or II studies specific for Hodgkin Lymphoma (defined in section 9.1). Total salvage combination chemotherapy must not exceed 2 salvage regimens.

Timing of HSCT:

- Admission for HSCT must be within 60 days from the last cycle of chemotherapy.

Organ Function and Performance Status Criteria:

- Karnofsky adult or Lansky pediatric performance score or ≥ 70
- Calculated creatinine clearance ≥ 50 ml/min/1.73m2
- Bilirubin < 2.5 (unless benign congenital hyperbilirubinemia), AST/ALT ≤ 3 x upper limit of normal
- Pulmonary function (spirometry and corrected DLCO) ≥ 50% normal
- Left ventricular ejection fraction or fractional shortening ≥ 45%
- Albumin ≥ 2.5.

Graft Criteria:

1. *Sibling donor*
   - Patients who have an HLA-matched or one allele mismatched related donor are eligible for entry on this protocol. This will include a healthy related donor who is genotypically or phenotypically matched at least 9/10 of the A, B, C, DRB1, and DQB1 loci, as tested by high resolution.
   - Donors will undergo a detailed medical history and physical exam.
   - Postpubertal female donors will be tested for pregnancy.
   - Clinical studies will include: CXR, EKG, CBC with differential and platelet count, PT/PTT, blood chemistries (complete biochemical profile), and must be within the normal range. Peripheral blood will be drawn for RBC typing and chimerism studies. Serologic testing for transmissible diseases will be performed per standard blood banking guidelines for organ and tissue donors; these presently include, but are not necessarily limited to $hepB_s$ Ag and hepatitis C antibody, HIV-1 and 2, HTLV-1 and 2, CMV and RPR. Serologic testing will be additionally performed to assess exposure to H. zoster, H. simplex, EBV, toxoplasmosis and West Nile Virus PCR. An HTLV/HIV(+) donor will be rejected on medical grounds.
   - Sibling donors must provide signed informed consent, to receive a 5-6-day course of G-CSF to mobilize PBSC and undergo two leukaphereses to donate PBSC.

2. *Unrelated donor*
   - Patients who do not have a related HLA-matched donor but have an unrelated donor who is matched at ≥ 9/10 (allele mismatch only) of the A, B, C, DRB1, and DQB1 loci, as tested by high resolution, will be eligible for entry on this protocol.
   - Unrelated donors identified by the NMDP may elect to donate either PBSC after treatment with G-CSF, or bone marrow.
   - Donors will undergo a detailed medical history and physical exam.

- Postpubertal female donors will be tested for pregnancy.
- Clinical studies will include: CXR, EKG, CBC with differential and platelet count, PT/PTT, blood chemistries (complete biochemical profile), and must be within the normal range. Peripheral blood will be drawn for RBC typing and chimerism studies. Serologic testing for transmissible diseases will be performed per standard blood banking guidelines for organ and tissue donors; these presently include, but are not necessarily limited to $hepB_s$ Ag and hepatitis C antibody, HIV-1 and 2, HTLV-1 and 2, CMV and VDRL. Serologic testing will be additionally performed to assess exposure to H. zoster, H. simplex, EBV, toxoplasmosis and West Nile virus PCR. An HTLV/HIV(+) donor will be rejected on medical grounds.
- Unrelated donors must provide signed informed consent, to receive a 5-6-day course of G-CSF and to undergo leukapheresis or undergo a bone marrow harvest. They will have their HSC or BM donations obtained at a qualified donor center participating in the NMDP.

3. UCB

- 2 UCB units will be selected according to current MSKCC unit selection algorithm. HLA testing to be done using molecular techniques: A and B antigen to at least intermediate resolution and DRB1 allele at high-level resolution.
- Each unit will be at least 4/6 HLA-A,B antigen and DRB1 allele matched with the recipient.
- In addition, each unit will have a cryopreserved dose of at least 1.5×10^7 total nucleated cells/recipient body weight (TNC/kg).
- Units with attached segments for confirmatory typing will be given preference.

6.2 Subject Exclusion Criteria

- Diagnosis: progressive disease at allograft work-up.
- Prior Therapy: prior allogeneic transplant or more than one prior autologous transplant.
- Cytoreduction and timing of HSCT: patients unable to complete planned cytoreduction due to therapy complications, or who undergo cytoreduction but are unable to proceed to allografting within the defined time period, are ineligible for allograft on protocol.
- Active and uncontrolled infection at time of transplantation including active infection with Aspergillus or other mold, or HIV infection.
- Inadequate performance status/organ function.
- Pregnant or breast feeding.
- Patient or guardian unable to give informed consent or unable to comply with the treatment protocol including appropriate supportive care, follow-up and research tests.

7.0 RECRUITMENT PLAN

Patients who fulfill the eligibility criteria as listed in Section 6.0 will be recruited for this study by an Attending Physician of the Lymphoma or BMT Service. Informed consent will be obtained by one of the participating investigators authorized to obtain consent. A copy of the signed informed consent will be placed in the medical record, as well as in the research file. Confirmation of patient eligibility will be done via the Clinical Trials Office.

Eligibility for the protocol should be determined by consultation with the physicians of the Lymphoma Service and the physicians of the Bone Marrow Transplant Service. For inclusion in the intention-to-treat component of the study, patients will be evaluated prior to salvage chemotherapy. The Lymphoma Service Physicians will decide upon the appropriate salvage chemotherapy, ensure the patient is an appropriate candidate for subsequent potential allograft, and contact the BMT service to initiate the donor search. Patients will then sign consent part I: Intention-to-Treat and proceed with salvage chemotherapy.

A suitable HSC graft will be secured during salvage chemotherapy. Once the graft is secured and salvage is complete, pre-allograft work-up and disease re-staging will be performed by the BMT Service as an outpatient. Eligible patients will be consented for allograft by the BMT service (consent part II) and then admitted to the Bone Marrow Transplant Unit for HSCT.

For the purposes of study enrollment complete remission (CR) will be defined as outlined in Section 12.5 whereas partial remission (PR) will be defined as $\geq$ 50% reduction of disease based on CT or PET criteria. Stable disease (SD) will be defined as absence of progression or < 50% reduction of disease based on CT or PET criteria. If there is a conflict between CT and PET responses, the PET scan will be used to define responses.

This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations. We expect that the study population will be fully representative of the range of patients referred for transplant without exclusion as to age, gender, or ethnic background within the limits of being able to identify a suitable HSCT graft. Pregnant women are excluded from participation in this study.

8.0 PRETREATMENT EVALUATION

8.1.1 Work-up prior to salvage chemotherapy

The following tests must be performed. Blood counts, chemistry, and disease assessment must have been performed within 30 days prior to starting salvage chemotherapy or less as clinically indicated:

- Complete history, review of systems, physical exam (including performance status) and informed consent.
- Bone marrow biopsy (trephine core) for morphology for documentation of disease status, as clinically indicated
- CBC with differential, comprehensive metabolic panel (CMP) including albumin, LDH, and serum uric acid.
- Measured creatinine clearance on 12-24 hour urine sample if any history of renal dysfunction or creatinine over 1.5.
- Urinalysis.
- EKG and echocardiogram with measurement of left ventricular ejection fraction. MUGA scan and/or response to exercise may be obtained as clinically indicated.
- CT scans: chest/abdomen and pelvis for disease staging and PET scans.
- Pulmonary function testing including DLCO.

- HLA Typing.

8.1.2 Pre-allograft work-up

The following tests must be performed. Blood counts, chemistry, and disease assessment must have been performed within 30 days (6 months for PFT and cardiac evaluations unless the patient has undergone additional therapy or has additional medical conditions that may affect pulmonary or cardiac function) prior to starting pre-transplant conditioning regimen or less as clinically indicated:

- Complete history, review of systems, physical exam (including performance status) and informed consent.
- Dental evaluation.
- Bone marrow biopsy (aspirate and trephine core) for morphology with surface markers, for documentation of disease status, as clinically indicated.
- CBC with differential, comprehensive metabolic panel (CMP), LDH, and serum uric acid. Basic coagulation profile. ABO Type and Screen.
- Urinalysis.
- Calculated creatinine clearance
- EKG and echocardiogram with measurement of left venticular ejection fraction. MUGA scan and/or response to exercise may be obtained as clinically indicated.
- Chest radiograph (within 60 days unless clinically indicated).
- CT scans: chest/abdomen and pelvis for disease staging and PET scans.
- Pulmonary function testing including DLCO.
- Serum testing for Cytomegalovirus (IgG and IgM), HIV-1/2, HTLV-1/2, toxoplasmosis, Hepatitis B (surface antigen, surface and core antibody), Hepatitis C, Herpes Simplex, Herpes Zoster, Epstein Barr Virus (EBV), syphilis.
- T lymphocyte immunophenotyping of peripheral blood (CD3/CD4/CD8) in patients who will receive double cord blood unit transplant.
- Pregnancy test for females of childbearing age.
- Peripheral blood to the Diagnostic Molecular Pathology Laboratory for chimerism studies (at any time pre-transplant).

9.1 TREATMENT/INTERVENTION PLAN

9.2 Salvage Chemotherapy

Eligible patients will receive 2-3 cycles of standard combination chemotherapy. This may include IGV,[14,15] MOPP, [32] or alternative regimens. In addition, patients may also be treated on ongoing MSKCC phase I or II studies specific for Hodgkin Lymphoma.

9.3 Involved-Field Radiation Therapy

In patients with a nodal mass greater than 5 cm that has not been previously irradiated and in the absence of extra-nodal disease, IFRT may be performed prior to allogeneic HSCT.

9.4 Allogeneic Transplant

Eligible patients will require a tunneled double or triple lumen central venous catheter and will be admitted to the Bone Marrow Transplant Unit or M9 for HSCT. Patients will be maintained in reverse isolation as per the allo BMT clinical care guidelines.

9.5 Reduced Intensity Conditioning Prior to HSCT: PR or SD Patients

Day	
-7	Admit and line insertion
-6	Fludarabine 30 mg/m^2 IV Melphalan 70 mg/m^2 IV
-5	Fludarabine 30 mg/m^2 IV Melphalan 70 mg/m^2 IV
-4	Fludarabine 30 mg/m^2 IV
-3	Fludarabine 30 mg/m^2 IV Start GVHD Prophylaxis
-2	Fludarabine 30 mg/m^2 IV
-1	Rest day
0	Transplant

Melphalan 70 mg/m^2 x 2 IV day -6 and -5 (2 doses)
Fludarabine 30 mg/m^2/dose IV days -6 to -2 (5 doses)

- Fludarabine:
    - Administer per MSKCC guidelines in the morning over approximately thirty minutes on days -6 to -2.
    - Do not administer IV Push
    - Fludarabine will be adjusted for decreased Creatinine clearance as follows:

Creatinine Clearance	Fludarabine dose
$\geq$ 60 ml/min	30 mg/m^2 x 5
50 – 60 ml/min	25 mg/m^2 x 5
< 50 ml/min	Ineligible

- Melphalan:
    - Administer per MSKCC guidelines on day -6 and -5 after the fludarabine is complete.
    - Do not administer IV Push
    - Infuse diluted product over a minimum of 15 minutes via a Secondary Administration set
    - Complete administration within 60 minutes of reconstitution

- Anti-emetics:
    - Aggressive anti-emetic prophylaxis must be used during the Melphalan. eg Zofran drip with additional prn medications as required.
    - Aprepitant (Emend^{TM}) should not be given during chemotherapy.

9.6 NMA Conditioning Prior for CR Patients

Day	
-7	Admit and line insertion
-6	Fludarabine 30 mg/m^2 IV Cyclophosphamide 50 mg/kg IV
-5	Fludarabine 30 mg/m^2 IV
-4	Fludarabine 30 mg/m^2 IV
-3	Fludarabine 30 mg/m^2 IV Start GVHD Prophylaxis
-2	Fludarabine 30 mg/m^2 IV
-1	TBI 200 cGy x 1
0	Transplant

Cyclophosphamide 50 mg/kg x 1 IV day -6
Fludarabine 25 or 30 mg/m^2/dose IV days -6 to -2 (5 doses)
TBI 200 cGy x 1 day -1

- Fludarabine:
    - Administer per MSKCC guidelines in the morning over approximately thirty minutes on days -6 to -2.
    - Do not administer IV Push
    - Fludarabine will be adjusted for decreased Creatinine clearance as follows:

Creatinine Clearance	Fludarabine dose
$\geq$ 60 ml/min	30 mg/m^2 x 5
50 – 60 ml/min	25 mg/m^2 x 5
< 50 ml/min	Ineligible

- Cyclophosphamide:
    - Administer per MSKCC guidelines with high volume fluid flush as per MSKCC guidelines.
    - Cyclophosphamide dose should be adjusted if patient is > 125% ideal body weight (IBW) and should be calculated on adjusted body weight per MSKCC standard of care guidelines.
    - High volume fluids should commence approximately 12 hours prior to the start of Cyclophosphamide and continue until 24 hours after the dose. Rate should be per MSKCC standard of care with diuretics as required to maintain fluid balance.
    - Electrolytes must be monitored twice daily on days -6 and -5.

- Total Body Irradiation: 200 cGy x 1 dose on day -1.

- Anti-emetics:

- Aggressive anti-emetic prophylaxis must be used during the cyclophosphamide.
- Anti-emetics for Cyclophosphamide should include scheduled 5 HT3 receptor antagonist (eg Zofran drip) with additional prn medications as required.
- Ativan™ can be used prior to TBI but only at low dose to avoid excessive sedation.
- Aprepitant (Emend™) should not be given during chemotherapy.

9.7 GVHD prophylaxis

All patients will receive GVHD prophylaxis as follows:

Recipients of related (RD) or unrelated donors (URD):

GVHD prophylaxis will be with Tacrolimus, Sirolimus and mini-methotrexate[33-35]

Day	
-3	Start Tacrolimus/Sirolimus
0	Transplant
+1	Methotrexate
+3	Methotrexate
+6	Methotrexate

Adults: *Sirolimus* will be given in a loading dose of 12 mg orally on Day –3 followed by a daily oral dose of 4 mg per day. Doses may be repeated if the subject vomits within 15 minutes of an oral dose.

Children: Children weighing < 40.0 kg will be given an oral loading dose of sirolimus of 3 mg/m^2 followed by a daily oral dose of 1 mg/m^2, rounded to the nearest full milligram.

Adults and Children: *Tacrolimus* will be given at a dose of 0.02 mg/kg every 24 hours as a continuous intravenous infusion beginning on Day –3. Convert the tacrolimus to oral dosing at 2-3 times the total 24-hour intravenous dose, split into 2 doses given every 12 hours as soon as clinically feasible.

Methotrexate will be given at a dose of 5 mg/m^2 intravenously on days +1, +3 and +6 to recipients of related or unrelated donors. The day +1 dose should not be administered until 24 hours after the BM or PBSC infusion. All doses of methotrexate should be administered unless life-threatening complications prevent administration. The BMT attending will determine if any MTX dose adjustments are necessary. IV folinic acid is NOT given after mini-methotrexate.

Methotrexate dose adjustment will be as follows:

HOLD: for Creatinine that doubles from admission AND is >2.0 mg/dl OR Creatinine >3.0 mg/dl (regardless of baseline Creatinine).

HOLD: for total Bilirubin > 3.0 mg/dl

MTX DOSE ADJUSTMENTS FOR WEIGHT: Use actual body weight for patients with BSA < 2.5 m^2, and adjusted body weigth for BSA > 2.5 m^2.

IMMUNESUPPRESSION WHEN MTX IS HELD: If a dose MTX is not given, another immune suppressant such as MMF 1gm IV q8 hours must be instituted.

Target serum levels and dose modifications

The target serum level for sirolimus is 3-12 ng/mL.

Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level. For levels < 3 ng/mL, unless clinically contra-indicated, the dose of sirolimus is to 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, but not required, that the dose be decreased by approximately 25% no more frequently than every 2 days until the target level is achieved. Alternatively, sirolimus can be held entirely as long as serum levels are monitored and the drug is restarted when the level returns to the therapeutic range and the treating physician feels it is appropriate to restart the agent. In patients where therapeutic levels cannot be achieved or maintained, alternative immunosuppressive drugs should be substituted.

The target serum level for tacrolimus is 5-10 ng/mL.

Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level. For levels < 5 ng/mL, the dose of tacrolimus will be increased by approximately 25% increments every 1-2 days, rounded to the nearest 0.5 mg (when dosing is oral) until the target range is achieved. Conversely, for levels > 10 ng/mL, the dose of tacrolimus will be decreased by approximately 25% every 1-2 days until the target level is achieved. Alternatively, tacrolimus can be held entirely as long as serum levels are monitored and the drug is restarted when the level returns to the therapeutic range and the treating physician feels it is appropriate to restart the agent.

Tapering

Tapering of sirolimus and tacrolimus will begin at Day 60 in the absence of GVHD and disease relapse. The goal of tapering is the complete discontinuation of immunosuppressant medications by 6 months or earlier if patients are in CR at transplant work-up (see below). Sirolimus and tacrolimus should be tapered in an alternating fashion every other week when clinically feasible. Similar reductions in dosages should be employed for each drug at each tapering event, with modifications at the end of the tapering schedule to allow near simultaneous discontinuation of sirolimus and tacrolimus.

Recipients of UCB:

GVHD prophylaxis will be with Cyclosporin A and MMF.

Day	
-3	Start CSA/MMF
0	Transplant

Patients will receive GVHD prophylaxis with 2 drugs as follows:

- **Cyclosporine A (CSA)** beginning on day -3 maintaining a level of 200-400 mg/L. The initial dose will be 2.5 mg/kg IV every 12 hours, over 2-4 hours as per MSKCC guidelines.
- Dose adjustments should be made on the basis of toxicity and low CSA levels with a trough level of < 200 mg/L.
- Once the patient can tolerate oral medications and has a normal gastro-intestinal transit time, CSA can be converted to an oral form.
- Patients will receive CSA for approximately 6 months. If no history or suspicion of GVHD, the dose should then be tapered with monitoring for development of GVHD and aiming to be off immunosuppression by 9-12 months after transplant if possible.
- Patients intolerant of CSA due to renal impairment or other toxicity aim for a lower level if possible. This can be done at the discretion of the treating physician. If unable to tolerate they may require tapering of CSA before MMF.
- Patients unable to tolerate CSA due to renal impairment or other toxicity should be considered for an alternative immunosuppressant in addition to mycophenolate mofetil as per MSKCC guidelines.
- In case of major CSA toxicity (eg CNS neurotoxicity documented by MRI), CSA should be discontinued. Patients may be re-challenged at a later date if clinically appropriate.
- For patients with GVHD, CSA may be continued for longer time periods according to standard of care guidelines.
- If disease progression or persistence occurs, or the patient is considered to be at very high risk of relapse, early taper or cessation of CSA can be considered with close observation for GVHD.

- **Mycophenolate mofetil (MMF)** should begin on day –3 at a dose of 1 gram IV q8 hours for patients who are > 50 kg. For patients < 50 kg, give 15 mg/kg IV q8 hours.
- MMF from day -3 to hospital discharge (must be at least day +14) should be IV. In preparation for discharge, switch to oral route (CellCept or generic mycophenolate mofetil, same dosing as IV) and round to tablet size.
- No dose adjustments for renal or liver disease are needed routinely unless severe organ dysfunction.
- Measurements of serum blood levels of MMF should be done routinely as per current MSKCC guidelines to guide assessment of potential MMF toxicity in the event of unexpected myelosuppression.
- If patient $\geq$ +28 days and without neutrophil engraftment, consideration can be made to reduce dosing to q12 after discussion with PI or co-PI. See MSKCC guidelines for further information about MMF levels.

- If no suspicion of GVHD, MMF can be tapered at approximately 75-100 days post-transplant. Keep the q8 dosing and taper at 10-25% decrements. The aim to be off the drug by approximately 4-6 months.
- Patients who are intolerant of MMF due to myelosuppression may require earlier but slow taper at the treating physician's discretion. Do not abruptly stop the drug unless life-threatening toxicity is suspected.
- If the patient is intolerant of CSA, MMF taper may be delayed.
- If the patient has acute GVHD requiring systemic therapy, MMF should only be tapered if control of GVHD has been obtained (eg resolution of skin rash, vomiting, and diarrhea), unless significant toxicity is attributed to MMF.
- If disease progression or persistence occurs, or the patient is considered to be at very high risk of relapse, early taper or cessation of MMF can be considered with close observation for GVHD.

For all patients (RD, URD, UCB)

For patients with GVHD, immunosuppression may be continued for longer time periods according to clinical care guidelines.

In patients not in CR prior to transplant, or if disease progression occurs, early taper or cessation of immunosuppression can be considered with close observation for GVHD.

9.7 Infusion of Sibling and Unrelated Volunteer Grafts

Beginning 5-6 days before the day of transplant, the normal donor will receive 10 mcg/kg of G-CSF, administered subcutaneously daily for at least 5 days. On the fifth and sixth days, the donor will undergo daily leukapheresis designed to provide 10^9 mononuclear cells per kilogram of recipient body weight. Mononuclear cell fractions will be pooled as collected, and will be assayed for CD34+ cell enumeration per standard procedures. The targeted dose of CD34+ donor PBPC to be infused is at least $5x10^6$ cells/kg.

If donor and recipient are ABO incompatible, appropriate red blood cell and/or plasma depletion will be performed. Thereafter, collected donor PBPC will be transfused by slow IV infusion, after suitable premedication as appropriate. Vital signs are to be obtained and documented before and after the infusions, and monitored during infusions as appropriate.

9.8 UCB Thaw and Administration

- UCB grafts will be received at the MSKCC Cytotherapy Laboratory prior to the start of the preparative regimen.
- Units will be thawed by and released from the Cytotherapy Laboratory according to current standards of practice (SOPs) and release criteria. As per standard practice, ABO blood group, total nucleated cells (TNC), CD34+ and CD3+ cell number and viability, sterility and colony-forming units (CFU) will be measured post-thaw.

- Units should be administered immediately upon arrival to the patient care unit by IV infusion by the nursing staff under supervision of a BMT attending physician. UCB infusion nursing guidelines should be followed.
- Units should be given consecutively as per nursing guidelines.
- Pre-medication should include acetaminophen and diphenhydramine or hydroxyzine dosed as appropriate for patient age. Do not give Hydrocortisone. Anti-emetics may be necessary and can be given prn.
- IV hydration equal to twice standard maintenance should be given for 6 hours prior to and at least 12 hours post UCB graft infusion with close monitoring of fluid balance, per MSKCC guidelines.
- IV Hydralazine should be used to treat hypertension associated with UCB infusion, if necessary.

Following infusion the bag and tubing from each UCB unit must be submitted to the Microbiology Laboratory. Specimen for Diagnostic Molecular Pathology will be forwarded by the personnel in the Cytotherapy Laboratory.

9.9 Growth Factor (G-CSF) after HSCT

G-CSF 5 mcg/kg/day IV/SQ (rounded to vial size to maximum of 480 mcg) will be given to all patients as from day +7 if absolute neutrophil count (ANC) is < 500. Continue until ANC is >2000 for 3 consecutive days. GCSF may be given earlier post transplant if clinically indicated at the discretion of the Attending Physician.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

10.2 Second line chemotherapy

Eligible patients will receive 2-3 cycles of combination chemotherapy as described in section 9.1. Following completion of chemotherapy and prior to allogeneic HSCT, patients may receive IFRT if indicated as described in section 9.2. The tests outlined below are part of routine care for patients receiving combination chemotherapy.

ACTIVITY	**TIMING**
History and physical	Approx. weekly
Chemistry	Weekly CMP
Counts/differential	Weekly

Disease evaluation (CT Scan, PET Scan)	Following 2nd or 3rd cycle

The remainder of this section applies to patients undergoing allogeneic HSCT.

10.3 Prophylaxis against Infection

Patients will be treated according to the allogeneic BMT standard of care guidelines and will be given prophylaxis against 1) bacteria during neutropenia, 2) Pneumocystis carinii, 3) Herpes simplex and Herpes Zoster, and CMV if recipient seropositive and 4) fungal infections. Patients who are Cytomegalovirus (CMV) seronegative pre-transplant should receive CMV seronegative blood products, except in an emergency. Patients will be closely monitored for activation of CMV and CMV viremia will be treated according to the allo BMT guidelines with ganciclovir or foscarnet.

10.3 Transfusions

All blood products for transfusion, with the exception of the stem cell graft, will be irradiated to 3,000 cGy to inactivate lymphocytes capable of initiating transfusion associated GVHD. Blood products are irradiated in the blood bank, using a cesium gamma emitter. Patients who are CMV-seronegative pre-transplant should not receive any CMV-seropositive blood products, except in an emergency. Platelets will be administered for clinical evidence of active hemorrhage and prophylactically in order to maintain a platelet count greater than 20,000. Packed irradiated red blood cells will be administered as clinically indicated.

10.4 Prophylaxis Against Menstrual Bleeding

Post-pubertal females will receive hormonal therapy to suppress menses unless a specific contra-indication to estrogen exists. This therapy may include Ovral™ (Ethinyl estradiol + norgestrel) daily at a dose of one daily tablet orally, estrogen patch +/- oral progesterone, or another regimen which has been successful for the patient. Hormonal suppression will continue until the platelet count is at least 50,000.

10.5 Nutritional Support

The physician will monitor nutritional status, and high-calorie parenteral alimentation will be given as needed. Vitamin supplements will be administered as clinically indicated.

10.6 Correlative Studies on UCB Units

Laboratory research studies will be performed using a maximum of 5% of each unit on the day of thaw investigating the determinants of (or factors associated with) unit predominance in patient engraftment. The correlative studies will include:

- Comprehensive characterization of the composition of each unit by flow cytometry (Clinical Laboratory, Supervisor Katherine Smith). This will include a basic analysis for CD34+, T, B,

NK cells (which is a standard of care and billable). In addition, studies of T regulatory cells, NK-T and dendritic cells will be performed (research non-billables). This can be performed on 8 million cells.

- Mixed lymphocyte cultures between the patient and each unit, and each unit against the other (Dr. James Young's Laboratory). This can be performed on 5 million mononuclear cells.

- Analysis of the Killer Ig-like receptor (KIR) genotype to assess if NK alloreactive cells are involved in unit predominance (Dr Katherine Hsu's Laboratory). This will be performed on the post Ficoll cell pellet and 34- cells not required by Dr Moore's laboratory.

- Assessment of stem cell potential of each UCB (Dr. Malcolm Moore's Laboratory). This will be performed on approximately 10-20 million mononuclear cells.

As a maximum of 5% of each unit will be used for research, these studies may be limited by the number of cells available. If the post thaw infused TNC is less than 1 x 10^7/kg per unit no cells will be taken from either unit for research purposes. Above if $\geq$ 1, a maximum of 5% of each unit will be taken. Experiments will be prioritized by the Principle Investigator according to the cell number available. Flow cytometry will take priority followed by a sample of mononuclear cells for Dr Young with the post Ficoll pellet going to Dr Hsu. Remaining cells will go to Dr Moore's laboratory. The results of the laboratory studies will be correlated with the engraftment of each unit in the patients (see Section 14.0).

10.7 Post Transplant Evaluation

Post-HSCT evaluations are summarized in the following table. Scheduled evaluations for day 21 may be performed +/-2 days, for day 28 may be performed +/-2 days, for day 60 and 100 may be done on +/-7 days, and for 6 and 9 months may be done +/-14 days, and 1 year, 2 years may be performed +/-30 days of the targeted date. Evaluations may be withheld if the treating physician feels that there is a strong contra-indication to perform the study (e.g. patient has relapsed and is terminally ill). Also, additional tests will be performed as clinically indicated.

ACTIVITY	TRANSPLANT TO DISCHARGE	DISCHARGE TO DAYS 100-120	LONG TERM FOLLOW-UP
Karnofsky score		+100	+6, 9, 12, 24 months
History and physical		Approx. weekly until day +100	+6, 9, 12, 24 months
Chemistry	Daily basic electrolyte panel with biweekly comprehensive metabolic panel (CMP)	Weekly CMP until day +100	CMP +6, 9, 12, 24 months

Counts/differential	Daily with differential when WBC ≥ 500	Weekly until day +100	+6, 9, 12, 24 months
BM aspirate with chimerism	Day +21 – core required (UCB) Day +28 (non-UCB)	Day +100 (if clinically indicated)	+6, 12, 24 months (if clinically indicated)
Chimerism: blood	Day +28	Day +60 (UCB only) Day +100	+6, 9, 12, 24 months
GVHD evaluation	Daily	Weekly	+6, 9, 12, 24 months
Disease evaluation (CT Scan, PET Scan)		+3 months	+6, 12, 18, 24 months
Immune recovery (per MSKCC standard)**		Day +60 (UCB)	+4, 6, 9, 12, 18, 24 months

** Note that immune recovery tests will not be required once patients have achieved documented immune recovery.

During the first 100 days patients will be closely monitored as per standard of care. Acute GVHD will be assessed and graded according to current MSKCC guidelines. To determine acute GVHD grading, clinical data will be collected at least every 2 weeks for the first 3 months.

Bone marrow aspiration with analysis for chimerism (DMP lab) must be performed on day 21 (UCB) or day 28 (non-UCB) to ensure donor hematopoietic engraftment. BM aspiration should be repeated subsequently if clinically indicated to monitor disease relapse and donor engraftment.

Additional blood (10-15 cc) will be obtained for follow-up research evaluations of immune recovery on approximately day +60.

10.8 Evaluation > 100 days post HSCT

These should include: history and physical examinations, blood counts and chemistries including liver function tests at a minimum of approximately every 6 weeks until 6 months, then at a minimum of approximately every three months for one year, and at approximately 3-6 month intervals until 2 years post transplant and then at least annually. The patient's referring physician, in consultation with the MSKCC transplant physician, may assist with follow-up.

Chronic GVHD will be diagnosed and graded according to current MSKCC guidelines. Assessments will be obtained at approximately day 100, 6 and 12 months, and annually after transplant and at additional time points as clinically indicated. Patients who develop chronic GVHD will be treated according to the current standard of care.

Bone marrow aspirate with analysis for chimerism and disease status should be performed at 6 months, one and two years post transplant, as clinically indicated.

Lymphoid immunophenotyping and function will be evaluated from 120 days as per MSKCC BMT standard of care guidelines. Patients will be vaccinated from 12 months after transplant as clinically appropriate and the response to vaccination should be documented.

11.1 TOXICITIES/SIDE EFFECTS

11.2 Toxicity Grading

Toxicities will be graded on a scale of 0 to 4 as described by the NCI- Common Terminology for Adverse Events (CTCAE), version 3.0.

11.1 Total Body Irradiation (TBI)

Likely

- The dose of TBI in this regimen is very low and therefore the side-effects that are associated with high doses of radiation should be minimal. At the dose of radiation in this study mild nausea and vomiting, diarrhea, mucositis, fever, transient erythema may occur but should be mild and can be treated symptomatically.
- Radiation contributes to the immune suppression induced by the chemotherapy and immune suppressing drugs. This is a major toxicity of the preparative regimen and is treated by donor stem cell infusion and aggressive supportive care.

Less likely

- High doses of radiation in combination with high dose chemotherapy may contribute to damage to vital organs such as the lung or the liver. This is sometimes associated with myeloablative conditioning and is not attributable to one specific agent. Such toxicity is highly unlikely with the doses in this protocol.
- Late effects include cataracts, second malignancies and hypothyroidism and are possible but unlikely due to the low radiation dose. Hypothyroidism will be routinely monitored post transplant and treated with hormonal replacement as indicated. Radiation could contribute to the risk for sterility that is primarily from chemotherapy. The risk increases with the number of years since puberty.

Dose Modifications

- There are no dose modifications.

11.2 Cyclophosphamide

Likely

- Nausea and vomiting: virtually all patients will experience nausea and vomiting after intravenous cyclophosphamide. This can be significantly diminished with anti-emetics.

- Diarrhea: most patients develop some diarrhea in the first week post cyclophosphamide. This is treated symptomatically.
- Myelosuppression and immune suppression is a major toxicity and is treated by donor stem cell infusion and supportive care.
- Alopecia is always seen but is usually reversible.
- Late effects include sterility.

Less Likely

- Hemorrhagic cystitis is a potential complication and can be variable in severity. Severe cystitis is unlikely. The risk of cystitis will be reduced by the administration of a high volume fluid flush during and 24 hours after drug administration. Fluid weight gain and edema is associated with this fluid flush but is transient and can be treated with diuretics if necessary.
- Syndrome of inappropriate anti-diuretic hormone (SIADH) can be seen but is transient and will spontaneously resolve after drug administration.

Rare but serious

- Cardiomyopathy has been described with cyclophosphamide but is very rare.

Dose Modifications

- There are no dose modifications.

11.3 Fludarabine

Likely

- Fludarabine may contribute to nausea, vomiting, mouth sores, and diarrhea which are primarily due to the cyclophosphamide.
- Jaundice and elevations of liver enzymes have also been described.
- Immune suppression is a major toxicity and is treated by donor stem cell infusion and supportive care.

Less likely

- Temporary erythema and desquamation

Rare but serious

- Effects on the nervous system are rare, but if they occur could include confusion, coma, weakness or numbness, loss of balance, difficulty walking, or loss of vision and could be very serious or lethal.

Dose Modification

- The dose will be modified based on Creatinine clearance as noted in section 9.

11.4 Melphalan

Likely

- Bone marrow suppression, complete ablation (bone marrow ablation is expected).
- Gastrointestinal: Nausea, vomiting, anorexia, diarrhea, stomatitis, esophagitis, colitis
- Alopecia

- Fever
- Transient liver dysfunction
- Renal or bladder dysfunction (increased BUN, creatinine, necrosis) may be seen.

Less likely
- Pulmonary fibrosis, respiratory distress, has been rarely reported.

Rare But Serious
- Serious hypersensitivity reactions: Edema, rash, anaphylaxis.

Dose Modifications
- There are no dose modifications.

11.5 Tacrolimus
- The major toxicity of Tacrolimus is immune suppression which leads to increased risk for infection. This is managed with aggressive supportive care with both prophylaxis and treatment of infectious complications.
- Renal dysfunction is common and is treated by good hydration and reduction of the dose if necessary. Electrolyte abnormalities involving potassium and magnesium are also common and electrolytes must be closely monitored.
- Increased blood pressure is common and is treated with anti-hypertensive medication(s).
- Neurological side effects: Tremor (common), seizures (rare), ataxia, cortical blindness (rare), and peripheral neuropathies.
- Gastrointestinal complaints including anorexia, nausea, and ileus.
- Other potential side-effects include liver toxicity, hyperglycemia, hirsutism, capillary leak syndrome (rare), hemolytic anemia (rare), and thrombotic thrombocytopenic purpura (rare). In addition there is an infusional toxicity from the cremaphor diluent. .

11.6 Sirolimus
- The major toxicity of Sirolimus is immune suppression which leads to increased risk for infection. This is managed with aggressive supportive care with both prophylaxis and treatment of infectious complications.
- The primary toxicities of sirolimus are hypertriglyceridemia, hypercholesterolemia, mild thrombocytopenia, anemia, leukopenia, hypokalemia, elevated LDH, arthralgia, epistaxis, edema, and infections.
- Clinically significant elevations in hepatic transaminases without sequelae were noted in the prior studies with this drug. However, the incidence of veno-occlusive disease of the liver was not noted to be higher than expected in trials of unrelated transplantation.
- A syndrome of thrombotic microangiopathy, comprised of microangiopathic hemolytic anemia, thrombocytopenia and renal dysfunction has been described in association with sirolimus and tacrolimus use.

11.7 Methotrexate

- Renal dysfunction: Decrease in creatinine clearance, renal wasting of magnesium and calcium, hypertension. Hypertension may be exacerbated by the concomitant use of corticosteroids.
- Hepatic dysfunction: Elevation in serum bilirubin and occasionally in serum transaminases.
- Mucositis: Mucositis secondary to the cytoreduction may be potentiated following the use of methotrexate post transplant.

11.8 Mycophenolate mofetil (MMF)

- The major toxicity of MMF is immune suppression which leads to increased risk for infection. This is managed with aggressive supportive care with both prophylaxis and treatment of infectious complications.
- Other potential side-effects include myelosuppression, headache, insomnia, aches and pains, rash, nausea, anorexia and diarrhea.
- There are no dose modifications.
- There is also a very rare side effect known as Progressive Multifocal Leukoencephalopathy (PML), which is a progressive disease of the nervous system that can cause severe disability or death. A very small number of cases of PML have been reported in patients treated with MMF. PML can cause hemiparesis, apathy, confusion, cognitive deficiencies and ataxia.

11.9 Cyclosporine-A (CSA)

- The major toxicity of CSA is immune suppression which leads to increased risk for infection. This is managed with aggressive supportive care with both prophylaxis and treatment of infectious complications.
- Renal dysfunction is common and is treated by good hydration and reduction of the dose if necessary. Electrolyte abnormalities involving potassium and magnesium are also common and electrolytes must be closely monitored.
- Increased blood pressure is common and is treated with anti-hypertensive medication(s).
- Neurological side effects include tremor (common), seizures (rare), confusion, ataxia, cortical blindness (rare), and peripheral neuropathies and are usually reversible with cessation of the medication.
- While mild to moderate microangiopathic hemolysis is relatively common, serious thrombotic thrombocytopenic purpura (TTP) is rarely seen.
- Gastrointestinal side-effects include anorexia and nausea, swollen gums, and hyperbilirubinemia.
- Skin changes include hirsutism and gingival hyperplasia.
- Dose may be modified for evidence of CSA toxicity.

11.10 G-CSF (Neupogen)

- Side-effects of G-CSF are generally mild, include bone pain, headaches, body aches, fatigue, edema and nausea and are managed with supportive care. Pleuro- or pericarditis are seen rarely and are managed by cessation of the medication and corticosteroids if necessary.

11.11 Mesna (Mesnex®)

- Mesna has no systemic side effects. Mesna is a uroprotectant and is being used concomitantly with the high dose cyclophosphamide. There are no dose modifications.

11.12 Blood product and HSC infusions

- Infusions of blood or HSC products may produce volume overload which can be managed with diuretics. They may also induce allergic reactions of variable severity, many of which can be prevented or mitigated by premedication with antipyretics, antihistamines, and narcotics. These products may also transmit serious infections (e.g., CMV, hepatitis, HIV). To circumvent this, donors are screened according to AABB and FACT guidelines. CMV antibody negative blood products will be used in CMV seronegative individuals whenever possible. All blood products (other than the HSC graft) are irradiated to circumvent the risk of GVHD caused by contaminating lymphocytes.
- Toxicities potentially associated with the infusion of the thawed UCB graft include DMSO toxicity and side effects from red cells and may include changes in heart rate or rhythm, changes in blood pressure, fever, chills, sweats, nausea/vomiting, diarrhea, abdominal cramping, headache, dyspnea, presence of DMSO taste and odor, hemoglobinuria, and acute renal failure. However due to hydration and pre-medication, severe toxicities are unlikely.

The definitions and reporting of serious adverse events (SAEs) is defined in Section 17.2.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.2 Primary Endpoint

The primary end-point of this study is the progression-free survival (survival without progression of malignant disease from what is present at pre-HSCT disease staging) at 1 year. Subsequent survival will be monitored as a secondary endpoint. Other important outcomes include:

12.3 Failure of Neutrophil Recovery and/or Donor Engraftment

As this is a reduced intensity or NMA allograft protocol neutrophil recovery after transplants and donor engraftment are not synonymous and must be considered separately. The following definitions will be used:

- The day of neutrophil recovery is the 1st day of 3 consecutive days of absolute neutrophil count (ANC) at or above 500 after the *1st* post-UCBT nadir.
- Donor chimerism will be defined as either partial (10-89% donor) or complete ($\geq$ 90% donor) and should be recorded as to whether it is sampled from the patient's marrow or peripheral blood. In the case of UCBT, record which UCB unit engrafts (by unit number). If both UCB donors engraft, the total donor chimerism (contribution of each donor added together) as well as the contribution of each donor individually should be documented.
- Primary graft failure = no neutrophil recovery by day 42 (regardless of donor chimerism) *or* autologous recovery (ANC recovery but < 10% donor in blood and BM) by day 42.

- Secondary graft failure = loss of ANC to < 500/μL for 14 consecutive days after initial recovery *or* loss of donor chimerism to < 10% donor after primary donor engraftment has been achieved not due to progressive malignancy within the marrow.
- Successful primary donor engraftment = neutrophil recovery within the first 42 days after transplant and partial/complete donor chimerism (≥10%).
- Successful sustained donor engraftment = successful primary donor engraftment without subsequent graft failure beyond 42 days. This will be reported along with the median (range) of total donor chimerism at serial time points post-UCBT.

Patients with suspected graft failure will be evaluated with bone marrow biopsy to assess BM cellularity and assess for residual or recurrent disease, culture for viral pathogens potentially causing graft failure including CMV and HHV6, and molecular analyses of marrow. Patients who suffer failure of donor engraftment will be managed with supportive care if they have autologous recovery and adequate hematopoiesis, or re-infused with autologous cryopreserved stem cells (if available) or a second HSC graft if they are aplastic.

12.4 Graft-Versus-Host Disease (GVHD)

Acute GVHD is manifested by skin rash, nausea, vomiting, diarrhea and ulceration of the intestines, hyperbilirubinemia and hepatitis, and suppressed or delayed recovery of the hematopoietic and immune system. Standard clinical criteria, and histological grading of skin, liver or gastrointestinal pathology where possible, will be used to establish and grade acute GVHD.

In the first 100 days after transplant patients will be assessed by a transplant physician for the development of acute GVHD approximately weekly. Data will be collected approximately every 2 weeks to characterize the severity of symptoms and signs caused by GVHD and to evaluate possible confounding factors. Data collection will include descriptive characteristics of rash and estimated body surface area involved, extent of dermal/epidermal separation, identification of concomitant causes of increased bilirubin other than GVHD, presence or absence of nausea, vomiting or anorexia persistent after engraftment, peak diarrhea volume with annotations concerning the presence or absence of urinary mixing and estimates of true diarrhea volume, presence of abdominal cramps or frank blood in the stool or melena, concomitant causes of GI symptoms other than GVHD, biopsy results, identification of any agents used for treatment and autopsy results if applicable.

Patients with moderate to severe acute GVHD (grade II-IV) will be treated in standard fashion with high-dose IV methylprednisolone as per standard of care. Patients failing to respond to steroids will be considered for treatment with standard or experimental immunosuppressive agents.

Chronic GVHD is characterized to varying degrees by sclerosis of lacrimal and salivary ducts, scleroderma-like changes of the skin, chronic inflammation and scarring of the gastrointestinal tract with consequent malabsorption and diarrhea, inflammation of the liver, suppression of the immune system and occasionally other auto-immune phenomena (eg auto-immune hemolysis) or involvement of other organs (eg pulmonary involvement). Chronic GVHD will be diagnosed and graded according to the criteria of Sullivan and treated with standard or experimental immunosuppressive therapy. Patients will be assessed for chronic GVHD at day 100, 6 months and annually after transplant, and more frequently if clinically indicated.

12.5 Transplant related mortality (TRM)

TRM is defined as death at any time from the commencement of pre-transplant conditioning due to any cause other than disease relapse with the exception of automobile or other accidents. The incidence of TRM at day 180 after allo transplant is a secondary end-point of the study. Also, stopping rules are in place to consider cessation of the study if TRM at day 100 after HSCT is in excess of 35%.

12.6 Disease Relapse or Progression

Relapse of malignancy, or progression of disease from the base-line documented pre-allo transplant, is a secondary endpoint of this study and will be defined by an increasing number of malignant cells of recipient origin in the marrow over 5%, by the presence of circulating malignant cells, pathologic lymphadenopathy or by the presence of malignant cells at any other site. Radiologic studies, flow cytometric analysis or molecular studies of the marrow and/or peripheral blood, and/or biopsy of lymph nodes or other sites may also be obtained for the diagnosis of relapse or disease progression.

Hodgkin's relapse or disease progression will be defined using CT and PET criteria:

Complete remission is defined as resolution of all disease related symptoms and normalization of PET scan and of bone marrow involvement on morphologic exam.

Partial remission (PR) is ≥ 50% decrease in the sum of product of diameters (SPD) of the 6 largest dominant lymph nodes and of sites of organ involvement, no increase in size or number of involved lymph nodes or organs, decrease in PET avidity.

Stable disease (SD) is less than PR but is not progressive disease.

Progressive/ relapsed disease (PD) is appearance of a new lesion ≥50% increase in SPD of more than one node or in greatest diameter of any previously identified node >1 cm in its short axis.

12.7 Immunologic Recovery

Immunophenotyping of T-cells, B-cells, and NK cells, and T-cell proliferations in response to non-specific mitogens and specific antigens, will be performed at serial time points after transplant to measure immune recovery. At approximately 60 days (2 months post-transplant) these will be performed only in UCB recipients and considered research studies as they will not guide clinical decision-making. From 4 months these studies will guide clinical decisions in terms of continuation of prophylactic antibiotics and are therefore both clinically indicated and billable. Patients will receive supplemental IV immunoglobulin (Ig) to prevent infection for at least 3 months post HSCT in recipients of UCB or URD donor and possibly longer if IgG levels are <

500. Subsequently, Ig levels will be tested at approximately 6, 12, 18 and 24 months post transplant to guide further IgG supplementation. Patients may be re-immunized as from 12 months post-transplant and the response to vaccination will be documented.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for patient/subject eligibility (eg a change in diagnosis), the patient will be removed from the study. Participants may be removed from the study if at any time it is determined to be in the participant's best interest to do so. Also patients may be removed from the study if requested by the patient. Management will depend on where they are in their treatment course. Such patients will receive appropriate supportive care.

14.1 BIOSTATISTICS

14.2 Clinical Endpoints

This is a phase 2 study of salvage chemotherapy followed by HSCT in patients with high-risk or relapsed Hodgkin Lymphoma. After treatment with salvage chemotherapy, patients that have a suitable donor and do not progress after the chemotherapy will receive an allogeneic HSCT. For this study, a patient will be classified as a success, if he or she obtains a response as a result of salvage chemotherapy, undergoes an allogeneic HSCT, and remains progression free for one year after HSCT. Pre-allograft conditioning will be determined by remission status post salvage chemotherapy assessed at the time of pre-allograft work-up. Patients who have stable disease or are in PR will receive a reduced intensity preparative regimen of Melphalan and Fludarabine (Mel/Flu). Patients in CR will receive a non-myeloablative preparative regimen of Cyclophosphamide, Fludarabine and low dose total body irradiation (Cy/Flu/TBI).

This is a revision of a phase 2 trial designed to investigate the efficacy and safety of salvage chemotherapy followed by HSCT in patients with high-risk or relapsed Hodgkin Lymphoma. In response to the slow accrual, the original treatment strata A (upfront patient not eligible for autologous transplant) and B (relapse after autologous transplant) were merged. For this study, a patient will be classified as a success, if he or she responds due to salvage chemotherapy, undergoes an allogeneic HSCT, and remains progression free for one year after HSCT. Currently, 5 of 15 patients are recorded a success on this study. These 15 patients are incorporated into a Simon two-stage minimax design that differentiates between success rates of 0.20 and 0.45. In the first stage, since more than 3 successes out of 15 patients were observed, an additional 9 patients will be accrued for a total of 24 patients. The salvage chemotherapy followed by HSCT would be considered worthy of further study in this patient population if 8 or more successes from the 24 patients were observed. This two-stage design has power 0.90 if the population success proportion is 0.45 and has a type 1 error equal to 0.10 at the success probability 0.20.

Patients with HL that are suitable for allograft but are referred for transplant after salvage chemotherapy is underway or complete may be transplanted on this protocol. While they will contribute to the allograft outcome data, they will not be part of the primary efficacy analysis described above. It is anticipated that approximately 6 patients will be treated through this course.

The maximum sample size for this study is anticipated to be 30 patients (24 on ITT study, and 6 transplanted without salvage chemotherapy administered on the protocol). The accrual period will be approximately 4-5 years with a follow-up period of 2 years post-transplant.
At the conclusion of the study, the Kaplan-Meier estimate of the progression free survival probability and the survival probability over time will be computed. Progression-free survival is defined as the time from the start of chemotherapy to the time of death, disease progression, or last follow-up. Kaplan-Meier estimates of progression free and overall survival will be computed for subsets of transplant patients (patients treated with salvage chemotherapy at MSKCC and all transplant patients), starting from the time of transplant. For the transplant subsets, the time to neutrophil and platelet engraftment, and the time to acute and chronic GVHD will be assessed using the cumulative incidence function. Also, the acute GVHD outcome by grade and the patient response to vaccination after allograft will be recorded for each patient and summary measures of these outcomes will be produced. The reasons for not receiving an allograft (lack of disease response to chemotherapy, no donor, or not fit for allograft due to treatment complications) will also be reported.

In order to reduce patient risk, the design includes a study evaluation boundary in the event of excessive day 100 TRM after HSCT during the accrual period. The boundary is derived using a repeated significance test and is summarized in the table below. If the boundary is crossed, it will be determined whether the treatment related deaths were composed of a well-defined subgroup of patients (e.g. the conditioning regimen). If this is found to be the case, the eligibility criteria for a future study may be refined to exclude these patients.

Table – Stopping boundary for day 100 TRM. Boundary based on an acceptable TRM rate of 0.15 and an unacceptable TRM rate of 0.40. The repeated significance test using this boundary has size 0.10 and power 0.90.

Stop if observe	5	Day 100 TRM within the first 15 patients
	6	20
	7	24

At the conclusion of the trial, the time to neutrophil and platelet recovery, the time to acute and chronic graft versus host disease, and the time to infectious complication, will be computed using the cumulative incidence function.

14.3 Laboratory Studies

Laboratory research studies will be performed investigating:

- The determinants of unit predominance to facilitate the understanding of the biology of double unit UCBT (see Section 10.5). The results of these studies will be correlated with the engraftment of each unit in the patients testing if the laboratory results predict or correlate with unit predominance in the patient. The Wilcoxon rank sum test will be used to test the

continuous correlates and the Fisher's exact test will be used for the binary correlates. The data collected on this protocol will be analyzed in aggregate with other clinical protocols of double unit UCBT.

- Immune recovery as measured by immunophenotyping of T-cells, B-cells, and NK cells, and T-cell proliferations in response to non-specific mitogens and specific antigens at serial time points after transplant. The results of these studies will be correlated with serious infectious complications. The Wilcoxon rank sum test will be used to test the continuous correlates and the Fisher's exact test will be used for the binary correlates.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation

17.1 PROTECTION OF HUMAN SUBJECTS

Risks: From the studies that have been done so far it appears that allo-HSCT can safely be performed in patients with advanced HL and that these patients may benefit from the treatment. However, given this is a new treatment approach, it is possible that there are side effects that have not yet been seen.

Benefits: The information from this study will help future cancer patients.

Possible toxicities/side effects: Toxicities and side effects of the agents used are listed in section 11 and reporting of serious adverse events is found in section 17.2.

Consent Process: Participation in this study is voluntary. All patients will be required to sign a statement of informed consent which must conform to MSKCC IRB guidelines.

Alternatives: Alternative treatment options will be presented to the patient prior to taking part in this study. Alternative treatment options may include getting treatment with either chemotherapy or a transplant without being on a study; taking part in another study; or getting no treatment.

Costs: The patient's health plan/ insurance company will need to pay for all of the costs of treatment in this study. The patient will be responsible for the costs of standard medical care, including the allograft, all hospitalizations and any transplant complications. Pre-authorization for allogeneic transplant will be cleared with the health plan/ insurance company prior to allograft admission. Patients will not be paid for taking part in this study. Once the cord blood units have been shipped, the patient's health plan/ insurance company will need to pay for the costs of the units even if they are not administered. Research tests will be done at no cost to the patient.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.
The report should contain the following information:
Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

The current study includes two treatment phases, salvage chemotherapy and HSCT. All patients will be followed for safety and toxicity related to the study. Toxicities will be graded using CTC guidelines (v3.0). This will occur during both treatment phases of the study. An adverse event is any adverse change from the patient's baseline (pretreatment) condition, including any clinical status change or clinically significant laboratory test value abnormality that occurs during the course of the clinical study whether it is considered related to the treatment or not.

For the 1st treatment phase of the study (salvage chemotherapy), elective hospitalizations to administer the cytoreduction regimen are not adverse events. Grade 3 or 4 neutropenia and/or thrombocytopenia will not be considered an adverse event unless its duration exceeds 28 days.

Potentially serious toxicities are an expected part of transplant therapy. However, for the purposes of this study, serious adverse events (SAEs) which will be reportable for the second part of the study (HSCT) will be defined according to the current MSKCC BMT program guidelines (Adult and Pediatric BMT Adverse Event Reporting Standard Operating Procedures, version 1.0 dated 1 December 2011).

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

Patients recruited to this study are individuals with high-risk or relapsed HL who are suitable allograft candidates. Prior to consideration for transplant, all patients undergo salvage chemotherapy, either at MSKCC or at an outside institution. Those patients receiving salvage chemotherapy at MSKCC are first required to sign part I of the informed consent in order to take part in the intention to treat portion of this study. Patients who received salvage chemotherapy at an outside institution do not take part in this aspect of the study and are not required to sign consent part I. All patients who do not have POD after salvage chemotherapy, and who have both suitable HSC donors and a satisfactory pre-allograft work-up sign part II of the informed consent and proceed to the allograft portion of the study. Patients who fail any of these 3 criteria will be off study and considered treatment failures. Pre-allograft conditioning will be determined by remission status post salvage chemotherapy assessed at pre-allograft work-up. Those patients with stable disease or in PR will be placed into study Arm A, the reduced intensity preparative regimen of Mel/Flu and those in CR will be placed into study Arm B, the NMA preparative regimen of Cy/Flu/TBI. Cytoreduction will be followed by transplantation using the best available donor (sibling PBSC, URD HSC or BM, or UCB).

Prior to consideration for this study, all patients undergo a series of consultations discussing the risks and potential benefits of salvage chemotherapy followed by allogeneic stem cell transplant

and the different procedures which are a normal part of the transplant course. The risks and potential benefits of the transplant procedure, as well as the participation in a research protocol are also discussed.

Only the principal investigator or the attending physicians named as consenting professionals and designated in section 15 will be qualified to conduct the informed consent process. They will explain the nature of the investigation and the risks involved to each patient prior to enrollment and will obtain written, informed consent. The patient will also be informed that he/she is free to voluntarily withdraw from study at any time.

All patients must sign three IRB-approved consent forms indicating their consent to participate. Sibling donors will also sign a consent form in triplicate, which reviews the risks and alternatives to G-CSF-elicited PBSC mobilization, and collection of PBSC via leukapheresis. Unrelated donors will provide written consent for marrow donation or HSC mobilization and collection according to the consent procedures of the National Marrow Donor Program.

The informed consent will meet FDA regulations, the requirements of 21 CFR 50.20 and contain the information required by each of the eight basic elements of 21 CFR 50.25 (a), and each of the six elements of 21 CFR 50.25(b) that is appropriate to the study. One original signed consent form will become part of the patient's medical record. Each patient will receive a copy of the signed consent form. The third consent form will be on file in the research file.

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