Roswell Park Cancer Institute

Protocol Number: I 72806 NCT00536601

Protocol Title: **AUTOLOGOUS BLOOD AND MARROW TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES AND SELECTED SOLID TUMORS**

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Amendment #9

Date: Feb 6, 2018

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1.0 ABSTRACT

Title: AUTOLOGOUS BLOOD AND MARROW TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES AND SELECTED SOLID TUMORS

P.I. Philip McCarthy, M.D.

Investigator-initiated Study

Pilot Study

Objectives: Examine the Progression Free Survival (PFS) by high dose therapy regimen for Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL). For the diagnoses of HL, Multiple Myeloma (MM) and NHL, examine the PFS for those who are at high versus standard risk for disease progression or relapse after BMT. For the diagnoses of Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML) both acute leukemias (AL), determine if the known prognostic factors can be used to group patients into high and standard risk groups.
Secondary Objectives: Examine the high dose therapy regimen-related toxicity (RRT) and overall survival after BMT for all groups. For purposes of reporting to the Center for International Blood and Marrow Transplant Research (http://www.cibmtr.org/) , all patients' disease status at transplant will be determined prior to initiation of protocol therapy. For purposes of analysis, patients will be stratified into groups (low (standard) and high-risk for recurrence), since accrual of patients to some of the individual disease/status strata will be slow.

Treatment Overview

Eligible patients with HL, MM, NHL, ALL, AML and selected solid tumors (primarily testicular cancer and neuroblastoma) will undergo stem cell collection and autologous stem cell transplant according to the study schema in Section 2.

Eligiblity Criteria

Disease Diagnoses: Histologically confirmed diagnosis of malignant hematologic disorders, Amyloidosis or solid tumor malignancy including recurrent or refractory disease or disease at high risk for recurrence including HL, NHL, AML, ALL, MM, and other lymphoproliferative disorders such as CLL and Waldenstrom's macroglobulinemia. Solid tumor patients include testicular cancer patients who have relapsed disease or primary progressive disease which is responding to salvage therapy; relapsed or advanced-stage newly diagnosed neuroblastoma pediatric patients; other patients with solid tumors who have recurred following conventional treatment or are at high risk

for relapse, and demonstrate chemosensitivity.

Subjects and Target Study Duration, Endpoints and Brief Statistical Section

This is a Pilot study of high dose therapy and autologous blood or marrow transplantation for patients with hematologic malignancies or disorders who have failed standard first-line chemotherapy or who are in their first remission, but are at high risk of relapse. Patients will be stratified into 6 disease groups (acute leukemia (AL), HL, NHL, MM, Amyloidosis, and solid tumors) for analysis of high dose therapy regimens. Response rates for each regimen will be determined separately for the individual disease strata. This is a total of 224 and this population size will allow for estimation of interest. The accrual rate of approximately 3 per month will allow for up to a total accrual of 252 over approximately 84 months.

The primary objective of this study is to determine the activity of the proposed blood or marrow transplant high dose therapy regimens. Response rates and toxicities will be reported using descriptive statistics. The Kaplan-Meier method will be used to construct progression-free and overall survival curves. Patients will be stratified into 6 disease groups. The Overall Survival and Progression Free Survival will be estimated in addition to response and toxicity rates.

2.0 STUDY SCHEMA

Figure 1a shows this study's schema:

Disease	High Dose Treatment	Estimated Accrual
Acute Leukemia (ALL/AML)	BuCy2iv	11
Acute Leukemia (ALL/AML)	CT6	10
HL	BuCy2iv	10
HL	CBV	25
NHL	BuCy2iv	35
NHL	CBV	35
Amyloid	Mel120	5
Amyloid	Mel200	20
Myeloma	Mel120	9
Myeloma	Mel200	50
Solid Tumor	Solid Tumor Regimens*	14

* Testicular Cancer, VCp (Tandem); Neuroblastoma or Small Round Blue Cell Tumor, TtC1500 followed by VCpM; Other Solid Tumors CTtCp. See Figure 1b for high Dose Treatment regimen abbreviations.

Figure 1b: High dose therapy regimens assigned by Disease, Age and co-morbidities:

Disease	Variables	Preferred Regimen (Old nomenclature)	Preferred Regimen (New nomenclature – Codes in the BMT database)
ALL	Any Risk, Radiation not contraindicated	CT	***CT6***
ALL	Any Risk, Radiation Contraindicated	BuC	***BuC2iv***
AML	Any Risk	BuC	***BuC2iv***
HL/NHL	Any Risk under the age of 60	CBV	***CBV***
HL/NHL	Any Risk over the age of 60	BuC	***BuC2iv***
MM or	Any Risk with adequate	M^{200}	***M200***

Disease	Variables	Preferred Regimen (Old nomenclature)	Preferred Regimen (New nomenclature – Codes in the BMT database)
Amyloidosis	organ function		
MM or Amyloidosis	Any Risk with compromised organ function	M^{120}	***M120***
Testicular Cancer	High Risk	VCp	***VCp (tandem)***
Neuroblastoma or small round blue cell tumor patients ≤ 30 years of age)	relapsed or advanced-stage newly diagnosed	Tt/C followed by VCpM	***TtC1500 followed by VCpM***
Other Solid Tumors (Not Testicular Cancer or Neuroblastoma)	High Risk	CTtCp	***CTtCp***

Abbreviations for new nomenclature:
CT6: Cyclophosphamide 60 mg/kg IV daily x 2 days (120 mg/kg total dose) and 6 fractions of TBI - 1200 cGy.
BuC2iv: Busulfan 0.8 mg/kg IV every 6 hours x 16 doses (12.8 mg/kg intravenous total dose) and Cyclophosphamide 60 mg/kg IV daily x 2 days (120 mg/kg total dose.)
CBV: Cyclophosphamide 1800 mg/m^2 IV daily x 4 days (7200 mg/m^2 total dose), BCNU 600 mg/m^2 x 1 dose and Etoposide 2400 mg/m^2 total dose continuously over 34 hours.
M120/M200: Melphalan 120 mg/m^2 x 1 dose; Melphalan 200 mg/m^2 x 1 dose.
VCp: Etoposide 750 mg/m^2 IV daily x 3 doses (2250 mg/m^2 total dose) and Carboplatin 700 mg/m^2 IV daily x 3 days (2100 mg/m^2 total dose),.
TtC1500: Thiotepa 300 mg/m^2 IV daily x 3 days (900 mg/m^2 total dose) and Cyclophosphamide (1500 mg/m^2 IV daily x 4 days (6000 mg/m^2 total dose) ***V/Cp/M***: Etoposide 200 or 300 mg/m2 IV daily x 4 days (1200 mg/m^2 total dose) and Carboplatin 375 mg/m^2 or AUC 4.1 IV daily x 4 days (1500 mg/m^2 total dose) and Melphalan 60 mg/m^2 IV daily x 3 days (180 mg/m^2 total dose) See section 8.4 for details
CTtCp: Cyclophosphamide 1500 mg/m^2 IV daily x 4 days (6000 mg/m^2 total dose) Thiotepa 125 mg/m^2 IV daily x 4 days (500 mg/m^2 total dose), and Carboplatin 200 mg/m^2 IV daily x 4 days (800 mg/m^2 total dose)

Etoposide Phosphate may be substituted for Etoposide in the event of anaphylaxis to Etoposide. Dosing is the same, volume is different.

3.0 BACKGROUND INFORMATION FOR STUDY

Autologous Blood and Marrow Transplantation (autoBMT) is the treatment of choice for selected patients with hematologic malignancies and solid tumors (Reviewed in Thomas' Hematopoietic Cell Transplantation). AutoBMT consists of collection of blood or bone marrow stem cells followed by intensive chemo/radiotherapy to treat and attempt to eradicate the patient's cancer. The appropriate intensive/chemotherapy regimen or high dose therapy regimens for selected diseases remain open questions as well as the appropriate patient population for autoBMT. Variables associated with the appropriate high dose therapy include type of chemotherapy and/or radiation. Patient variables include age, performance status, underlying organ function, disease, disease status at transplant and chemosensitivity.

The major problems associated with autoBMT include; regimen-related toxicity and relapse of the underlying malignancy. We have attempted to limit autoBMT-associated mortality while preserving the anti-tumor effect of the intensive therapy by closely examining the high dose therapy regimens. Patient characteristics are important in determining the response to and cure from autoBMT. Patients with chemotherapy -sensitive are more likely to benefit from autoBMT than those with resistant disease. However selected patients with chemotherapy-resistant disease such as Hodgkin Disease do benefit from autotransplant.

The RPCI BMT program has accrued patients to the current autologous BMT protocol (DS 91-15) since 1991. The target accrual of 450 patients will be met this year and the proposed study will replace DS 91-15. As of July 5, 2005, 419 patients had been enrolled to DS 91-15. Patients were stratified by risk for analysis as follows in Table 1:

Table 1

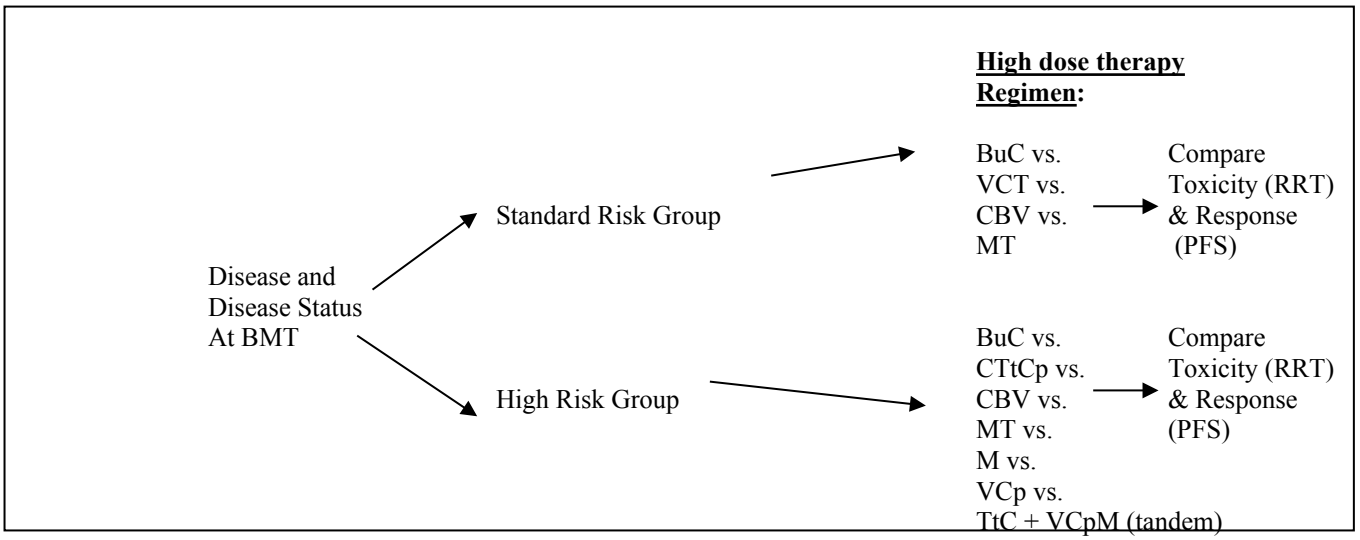
Standard Risk	Acute Leukemia in 1st Complete Remission (CR)
	Lymphoma in 1st or 2nd CR
High Risk	Leukemia and Lymphoma >2nd CR Resistant 1st Relapse Primary Refractory Disease*
	Multiple Myeloma
	Amyloidosis
	Recurrent or Primary refractory Testicular Cancer
	Other Solid Tumors

***** Refractory to standard chemotherapy

Results of DS 91-15 (Former Autologous BMT protocol):

The previous protocol was based on a disease and risk-adapted therapy for high dose therapy regimen selection. This schema is demonstrated below in Figure 2.

Figure 2



Abbreviations:
C: Cyclophosphamide, ***B***: BCNU (carmustine), ***V***: Etoposide (VP-16), ***Tt***: Thiotepa, ***Cp***: Carboplatin, ***T***: Total body irradiation, ***Bu***: Busulfan, ***M***: Melphalan, ***RRT***: Regimen-related toxicity grade 3 -4, ***PFS***: Progression Free Survival, OS = Overall Survival

Regimens were assigned by disease as follows:

Table 2

DISEASE	VARIABLES	PREFERRED REGIMEN
AML, ALL	any risk	MT
	radiation contraindicated*	BuC
Hodgkin's' Disease	any risk	CBV if <60 years old; BU/CY if ≥60 years old
Non-Hodgkin's' Lymphoma	standard risk under the age of 60	VCT
	prior exposure to VP/CY and under the age of 60	MT
	radiation contraindicated	BuC

DISEASE	VARIABLES	PREFERRED REGIMEN
Multiple Myeloma or Amyloidosis	any risk	M (100 per M^2 for those with organ toxicity, 200 per M^2 if adequate organ function
Testicular Cancer	recurrent or primary progressive disease	VCp
Neuroblastoma or small round blue cell tumor patients $\leq$ 30 years of age	relapsed or advanced-stage newly diagnosed	TtC followed by VCpM
Solid tumors, testicular	any stage	CTtCp

AML: Acute Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia.
***** For children under 16, BU/CY may be utilized.

Patient Accrual (through 7/5/2005).

Table 3

	Number	Percent
Acute Leukemias	29	6.9
Amyloidosis	9	2.1
CML	5	1.2
HL	64	15.3
MM	119	28.4
NHL	140	33.4
Solid Tumors	53	12.6
Total	419	100

Accrual was initiated in 1991. The protocol was modified in 1997 changing the delivery of radiation, dose of radiation and chemotherapy, as well as the regimen combinations. Diseases treated included: Acute Leukemias, Amyloidosis, HL, NHL, MM and selected solid tumors. Acute Leukemia patients consisted of patients with AML (n=28) and ALL (n=1) and have remained consistent. The frequency of transplant for amyloidosis has increased to approximately 2 per year. HL and NHL accruals have remained consistent. MM transplants have decreased this past year to approximately half of the previous annual accrual. The Solid Tumor numbers consist of 43 breast cancer patients who no longer would be offered transplant. The remaining 10 patients are those with neuroblastoma, testicular cancer and primitive neuroectodermal tumors.

Toxicity

We have demonstrated that the regimens in this study can be safely administered with acceptable toxicity: The day 100 toxic death rate is 5.5% (23/419). The day 100 toxic death rates for standard and high risk patients were 1.4% (1/71) and 6.3% (22/348) respectively. These toxic death rates are acceptable when compared to data from the Center for International Blood and Marrow Transplant Research (CIBMTR). The early stopping rules (based on a high day 100 toxic mortality rate) were not violated for this study. Secondary endpoints were incidence of severe to fatal regimen-related toxicity (RRT), graft failure/failure to engraft and secondary malignancy. Some patients developed more than one toxicity.

Table 4

Toxicity	Standard Risk Transplants	High Risk Transplants	All Transplants
Total number (percent)	71 (100%)	348 (100%)	419 (100%)
RRT grade 3 or 4	6 (8.5%)	33 (9.5%)	39 (9%)
Graft failure or failure to engraft	1 (1.4%)	2 (<1%)	3 (<1%)
Secondary Malignancy	2 (2.8%)	5 (1.4%)	7 (1.7%)
Day 100 Toxic Death Rate	1 (1.4%)	22 (6.3%)	23 (5.5%)

RRT: Regimen-related toxicity (defined by the Bearman criteria: J Clin Oncol 6 (10): 1562-8, 1988)
Graft failure: defined as patient's absolute neutrophil count falling to $<500/mm^3$ not due to disease progression after previous documented engraftment; Failure to engraft: defined as patient survival to day 60 with absolute neutrophil count $<500/mm^3$; Day 100 Toxic Death Rate: percent of patients who died before day +100 post-transplant due to transplant-related causes including: RRT, GVHL, Infection, Hemorrhage, graft failure/failure to engraft. Excludes the deaths before day +100 due to disease progression.

Outcomes

Response data for eligible patients who were evaluable for response as of July 5, 2005 are listed below:

Table 5

	Std Risk	High Risk	Total Pts
Total Number Entered	71	348	419
Total number evaluable	70	313	383
Number of Complete Responses	62	206	268
Number of Partial Responses	1	21	22
Number of Stable Responses	1	70	71
Number of Progression of Disease	6	16	22
Number of No Response	0	0	0
Number Too Early to evaluate	1	4	5

Figure 3

Progression Free Survival by Risk Group, Protocol DS 91-15

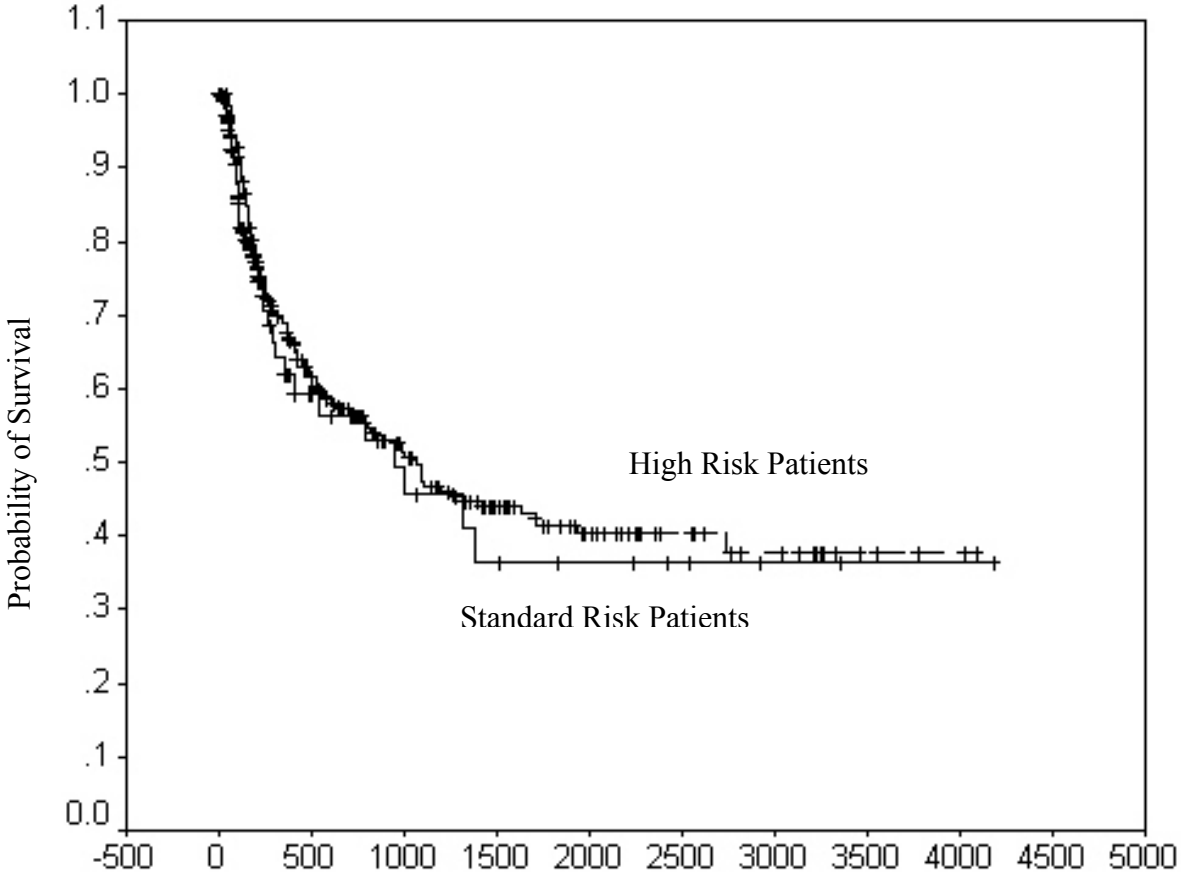


Figure 3: Legend for Progression Free Survival by Risk Group DS 91-15: Standard and High Risk patients are defined in Table 1.
Explanation: Solid line indicates patients who were at standard risk for relapse (n=70 evaluable patients). Dashed line indicates patients who were at high risk for relapse (n=335 evaluable patients). Nine patients (all high risk) with 2 transplants had one BMT excluded so that each patient is included only once. Five BMTs (1 standard risk, 4 high risk) were also excluded for PFS because they are too early to evaluate for best response to BMT.

Conclusion: There was no difference in Progression Free Survival by high risk and low risk stratification. P>0.8. Thus the risk stratification as defined in DS 91-15 has not proven to be predictive for PFS.

Figure 4

Progression – Free Survival by High dose therapy Regimen, Protocol DS 91-15

NON-TBI containing high dose therapy regimens:

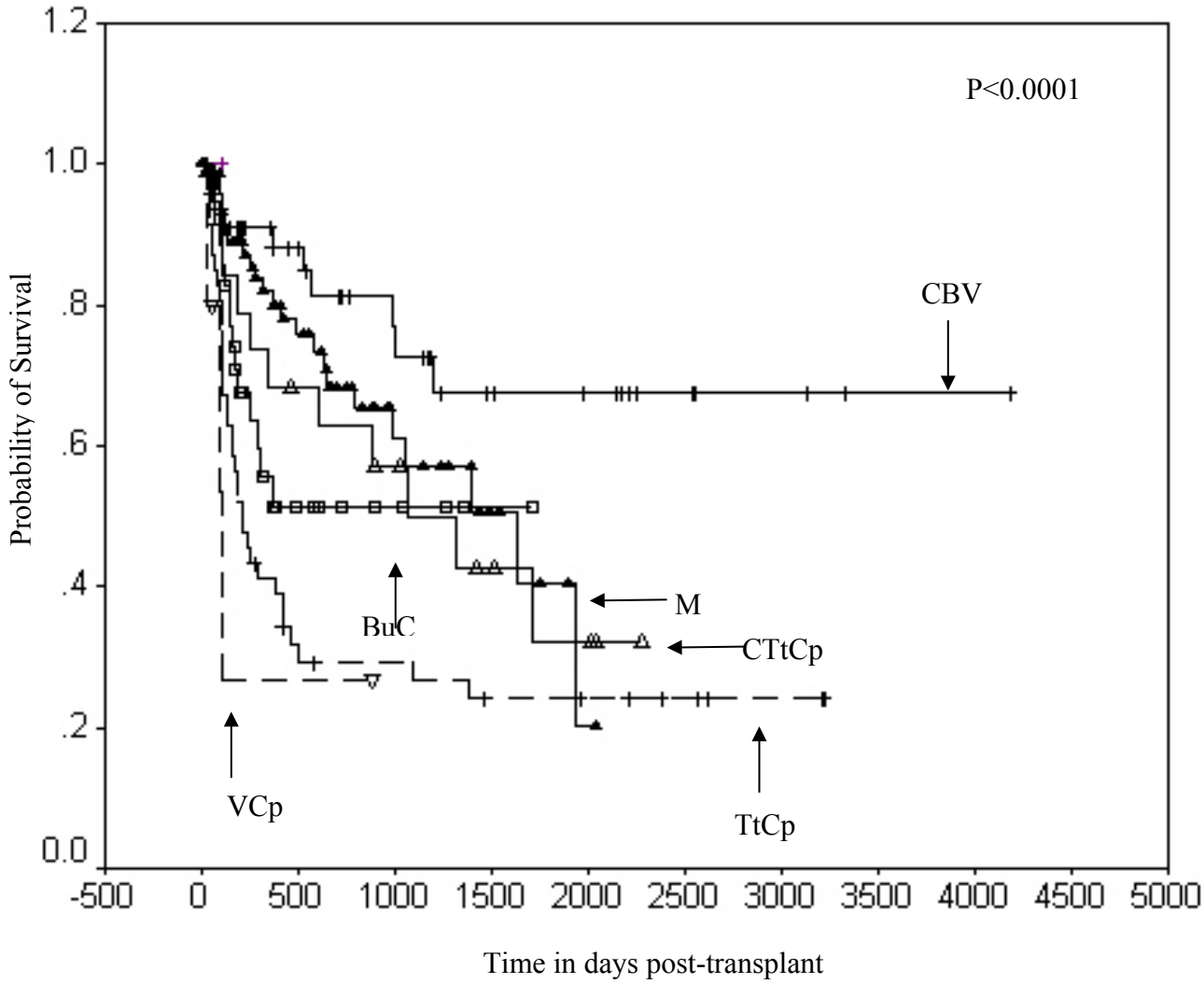


Figure 4: Legend for Progression Free Survival by Risk Group DS 91-15: B: BCNU (Carmustine); Bu: Busulfan; C: Cyclophosphamide; Cp: Carboplatin; M: Melphalan; Tt: Thiotepa; V: VP-16 (Etoposide).
Explanation: CBV has been used primarily for HL patients. M for myeloma patients, BuC for NHL patients over 60 years of age or if TBI contraindicated. TtCp, VCp, CTtCp were used for solid tumor patients. VCp is used for testicular cancer patients only. CTtCp is used for solid tumor patients excluding neuroblastoma and testicular cancer patients. TtCp is no longer used.

Figure 5

Progression – Free Survival by Diagnosis, Protocol DS 91-15

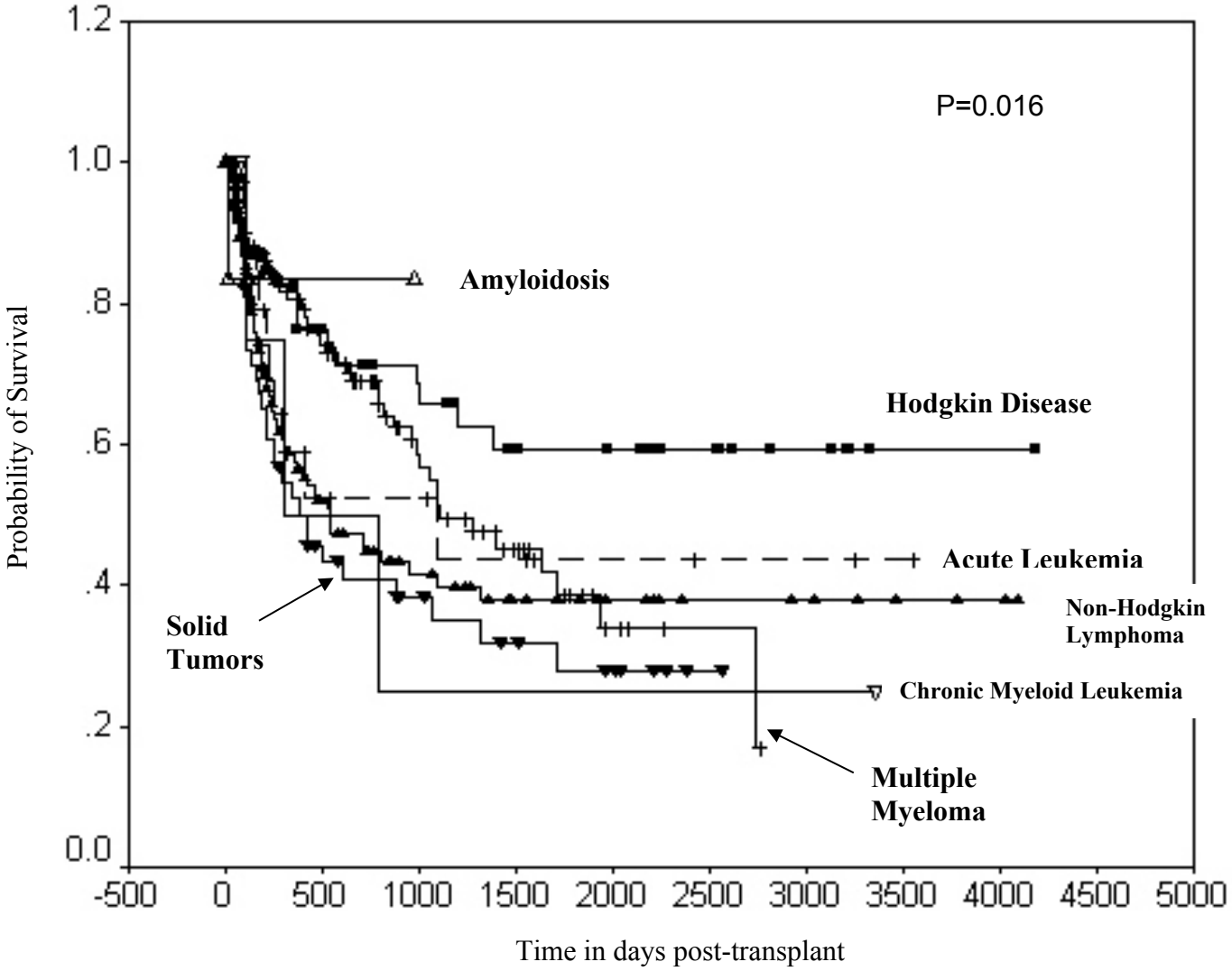


Figure 5: Legend for Progression Free Survival by Diagnosis DS 91-15: Amyloidosis (n=9) and HL (n=64) have the highest rates of PFS. Acute Leukemias (n=29), NHL (n=140) Solid tumors (n=53) and MM (n=119) have similar PFS. CML patients (n=5) have not been transplanted on this protocol since 1996

Hodgkin Lymphoma (HL)

Examining patient outcomes by disease, we found a PFS and OS of approximately 60% for HL patients receiving CBV. This is equivalent or superior to results reported to other series that have examined CBV as the high dose therapy regimen during autotransplant (Salar et al). Figure 6

demonstrates that CBV is a superior regimen to thiotepa-based regimens (Thiotep and Total Body Irradiation and Thiotepa and Carboplatinum). The Thiotepa regimens have been discontinued as high dose therapy regimens. We will continue to use CBV for HL patients who are less than 60 years of age. CBV is a moderately toxic regimen especially for older patients and BuC was used for patients 60 years and older. There were not enough HL patients receiving BuC to analyze therefore it will be used for those older than 60 years. An objective of this protocol is to compare the efficacy (PFS) of CBV vs. BuCy2iv in HL patients.

We developed and published the use of a prognostic model for outcome based on HL patient characteristics immediately prior to BMT (Hahn et al, 2005). The 3 factors associated with shorter event –free survival (EFS) prognosis were chemotherapy-resistant disease, Karnofsky Performance Status (KPS) < 90% and ≥ 3 chemotherapy regimens pre-BMT. Patients with 0 or 1 prognostic factors are considered low risk and those with 2 or 3 prognostic factors are considered high risk. We will use these prognostic factors when available to determine patients at high risk for poor BMT outcomes. If the model continues to remain valid, this will corroborate the need for alternative approaches to the high risk population such as a more intensive high dose therapy regimen or an alternative approach such as allogeneic BMT.

Figure 6

Progression – Free Survival For HL Patients by Regimen, Protocol DS 91-15

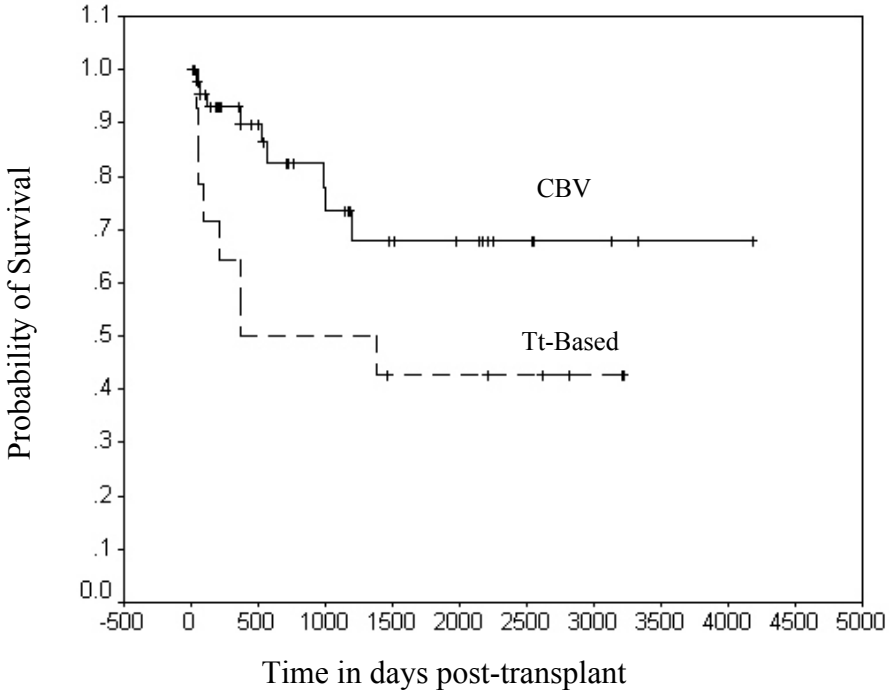


Figure 6 Legend: Progression-free survival for HL patients treated on DS 91-15 comparing TtT or TtCp (dashed line, n=16) vs. CBV (solid line n=46), p=0.0295. Thiotepa-based regimens are significantly inferior to CBV and are discontinued for use in HL.

Non-Hodgkin Lymphoma (NHL)

Several regimens have been used for autotransplant (Hahn et al 2001). RPCI regimens include VCT, TtCp, MT, TtT and BuC. BuC was recently added for patients 60 years of age and older and for those who could not receive a TBI containing regimen. VCT has been the primary TBI-containing regimen for NHL patients since 1997. When we examined the PFS and OS for BuC and VCT, there was a trend toward an improved PFS in the BuC group however this was not statistically significant (see Figure 7). There is no difference in OS for VCT versus BuC. There has been no conclusive evidence that one regimen is superior. Chemotherapy-containing regimens may generate superior outcomes than TBI-containing regimens however this is not conclusive. (Salar et al, Peniket et al). In addition, TBI containing regimens appear to generate more toxicity. These toxicities are manifested by increased mucositis, lung toxicity and as well as secondary hematologic disorders including myelodysplastic syndrome and secondary Acute Myeloid Leukemia (AML). Thus, based on data from 91-15, that multi-drug non-TBI containing regimens may have superior efficacy to TBI containing regimens, CBV will be used for NHL patients under the age of 60 and those 60 years and older will receive BuC. CBV has a PFS of about 70% in HL patients, however CBV was used in only 3 DS 91-15 NHL patients, therefore a comparison of CBV in NHL patients cannot be made at this time. We will compare the CBV and BuC patient groups with historical populations receiving TBI containing and non-TBI-containing regimens. An objective of this protocol is to compare the efficacy (PFS) of CBV vs. BuCy2iv in NHL patients.

Vandenberghe et al published registry data demonstrating that autotransplant for mantle cell lymphoma patients in 1st CR resulted in a Progression Free Survival of greater than 50% at 5 years. This is superior to results with standard chemotherapy. There have been no randomized trials comparing autotransplant versus standard chemotherapy. Thus, MCL patients will be offered auto BMT in first CR.

Peniket et al have demonstrated that autologous BMT is associated with a lower morbidity and regimen related mortality than allogeneic BMT. However allogeneic BMT is associated with a lower relapse rate. Until the mortality associated with allo BMT is decreased, autologous BMT will be the preferred treatment unless the patient has high risk features more suitable for allo BMT. These include patients who do not attain a CR with salvage therapy and all NHL patients who relapse after autotransplant.

Figure 7

Progression – Free Survival For NHL Patients by Regimen, Protocol DS 91-15

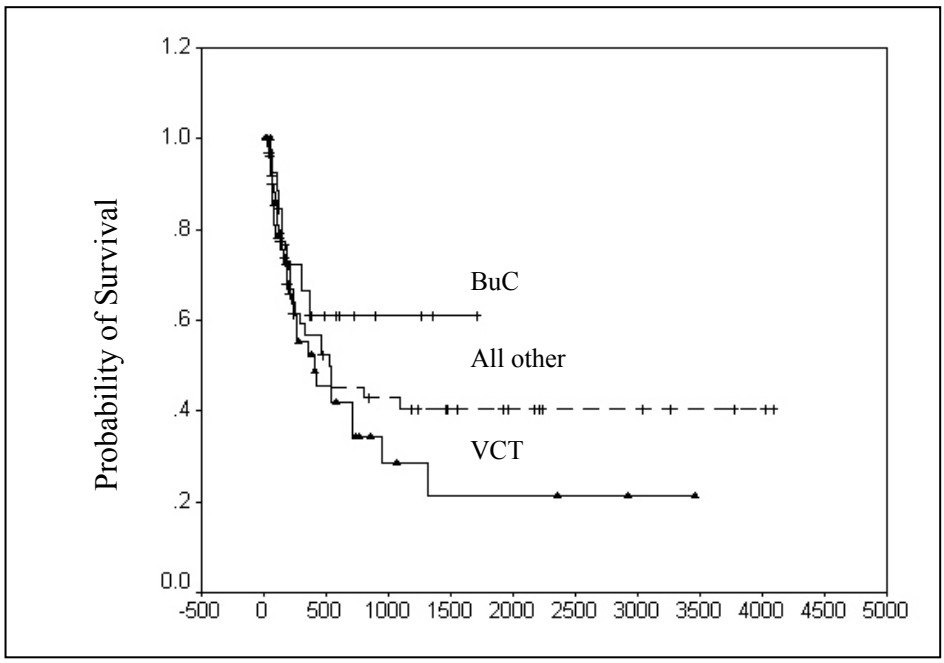


Figure 7 Legend: Progression-free survival for NHL patients treated on DS 91-15 comparing BuCy2iv (solid line, hatched tick mark, n=27) vs. other high dose therapy regimens (dashed line, n=62) vs. VCT (solid line, closed triangle tick mark, n=45), p>0.05. Other high dose therapy regimens included TtCp, TtT, and MT. VCT-based and other high dose therapy regimens will no longer be used in NHL patients.

Multiple Myeloma and Amyloidosis

BMT remains the standard of care for myeloma patients responding to initial therapy or in those who progress after response to initial therapy (Attal et al, Child et al Hahn et al 2003). We had previously used Melphalan (M) only at a dose of 140 mg/m^2 for patients above the age of 60 due to concerns regarding toxicity at a dose of 200 mg/m^2. This cutoff was changed to age 65 in January, 2005 without deleterious effect. Patients who are above the age of 65 can be treated with higher doses of melphalan up to 200 mg/m^2 (Reece et al). In addition, M was used in combination with total body irradiation (T) until February, 2002. The use of MT was stopped when a randomized study demonstrated there was no difference in outcome when compared to M alone (Moreau et al). Our results confirm this finding as shown in Figure 8. For this protocol, M will be used at a dose of 200 mg/m^2 for patients who have no evidence of organ dysfunction regardless of age. This regimen is also safe for patients with amyloidosis without serious underlying organ dysfunction (Working Group of UK Myeloma Forum). For patients with underlying organ dysfunction, we have

historically utilized M at a dose of 100 mg/m^2. This has included patients who are in renal failure and those with cardiac dysfunction and it has been well-tolerated in patients who would otherwise not receive a BMT. In an effort to increase the efficacy of the M, the regimen will be increased to 120 mg/m^2 for all patients who are otherwise not eligible for M at a dose of 200 mg/m^2.

In an effort to determine risk and assess outcome following BMT, we will utilize a new scoring system (when available) that is based on diagnostic criteria. This simple outcome scoring system uses serum Beta-2 Microglobulin (β2M) and serum albumin at diagnosis for determining prognosis and is described as follows (Greipp et al):

> Stage I, Serum β2M < 3.5 mg/L and serum albumin ≥ 3.5 g/dL (med. survival, 62 months);
> Stage II, neither stage I nor III (median survival, 44 months)
> Stage III, Serum β2M ≥ 5.5 mg/L (median survival, 29 months).

This staging system will be used for assigning risk before BMT (by measuring this at time of BMT). In addition, we will score patients with available data at the time of BMT to determine if this will be a useful prognostic score at time of BMT in addition to at time of diagnosis.

Objectives of the section of the protocol will be to compare the utility of this staging system and to determine the toxicity of the M regimen in an older age population as well as the increase M dose for patients who would otherwise not have received a BMT in the past.

Figure 8

Progression – Free Survival For MM Patients by Regimen, Protocol DS 91-15

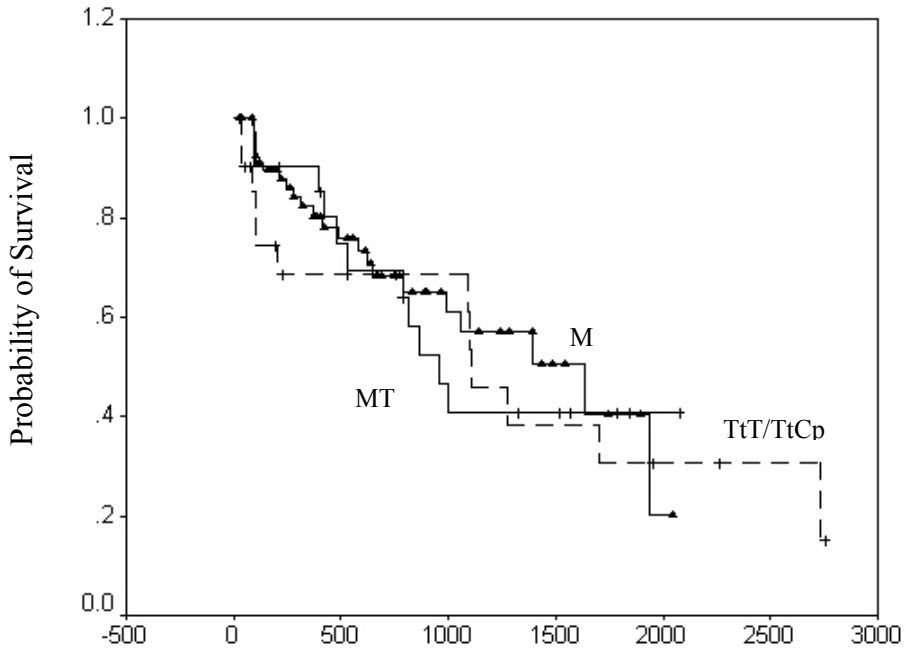


Figure 8 Legend: Progression-free survival for MM patients treated on DS 91-15 comparing M (solid line, closed triangle tick mark, n=71) vs. MT (solid line, hatched tick mark, n=21) vs. TtT/TtCp (dashed line, n=22), p>0.05. TtCp, TtT and MT high dose therapy regimens are no longer used in MM patients. M was used at varying doses of 100, 140 or 200 mg/m^2 in DS 91-15 MM patients.

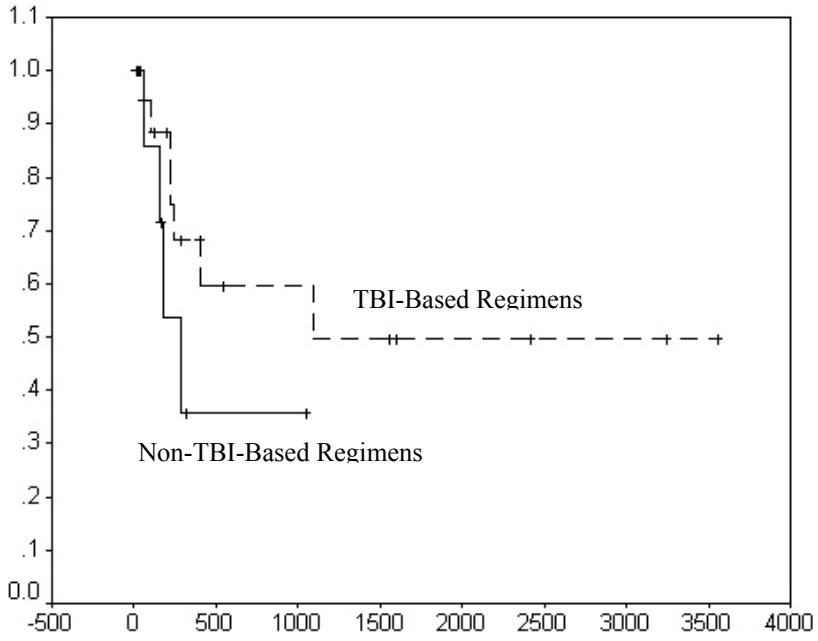
Amyloidosis is an incurable plasma cell disorder that results in deposition of amyloid protein in the form of light chains. There is no standard conventional therapy for Amyloidosis patients. Approximately 40% of Amyloidosis patients respond to autologous BMT (Comenzo et al). Amyloidosis patients will be treated on this protocol with doses of M at 120 and 200 mg/m^2 depending on underlying organ function.

Acute Leukemias

Autologous Blood or Marrow Transplant have been utilized for the treatment of acute leukemia since the 1958 (McGovern et al). It was in the 1970s and 1980s when this form of therapy became more established as a therapy for patients who did not have suitable donor for allogeneic transplantation (Reviewed in Thomas' Hematopoietic Cell Transplantation). VCT, MT, TtT and BuC have all been used as high dose therapy regimens for acute leukemias, in first or second CR. BuC has been used for older patients and those who cannot receive total body irradiation (TBI). In an attempt to standardize the regimens, all acute leukemia patients who are younger than 65 years of age will receive CT. Those Acute Leukemia patients who are 65 years of age and older will receive BuC for high dose therapy.

Figure 9

Progression – Free Survival For Acute Leukemia Patients by Regimen, Protocol DS 91-15



Progression-free survival for Acute Leukemia patients treated on DS 91-15 comparing Total Body Irradiation (TBI)-based high dose therapy regimens (dashed line, n=21) vs. non-TBI-based high dose therapy regimens (solid line, n=7), p>0.05. A variety of TBI and non-TBI regimens were used, with small patient numbers in each group, making comparisons of superior high dose therapy regimens impossible. An objective of this protocol is to compare the efficacy (PFS) of using consistent standardized high dose therapy regimens of CT (TBI-based) vs. BuCy2iv (non-TBI based) in Acute Leukemia patients.

Solid Tumors

Solid tumor patients have been treated with different regimens including TtCp as well as CTtCp. On protocol DS 91-15, there were 43 breast cancer, 5 testicular cancer, 1 PNET and 1 neuroblastoma patients who received autologous transplants. Breast cancer patients are no longer treated with autologous BMT. The other diseases have too few historical patients to provide comparative PFS curves. With the exception of neuroblastoma patients and testicular cancer patients, all eligible solid tumor patients will receive CTtCp for high dose therapy for BMT. Neuroblastoma patients will receive a tandem transplant with TtC followed by CpVM. Testicular cancer patients will also receive a tandem transplant consisting of VCp given twice.

4.0 STUDY PURPOSES AND OBJECTIVES

Primary Objective:

1) Estimate the Progression Free Survival (PFS) distribution for HL, NHL and MM for each disease-specific high dose therapy regimen.

Secondary Objectives

1) Estimate the PFS distribution for Amyloidosis, Acute Leukemia and Selected Solid Tumors for each disease-specific high dose therapy regimen.

2) Explore the role of risk factors in the outcome of all treated patients

3) Examine the high dose therapy regimen-related toxicity (RRT) and overall survival after BMT.

For purposes of reporting to the Autologous Blood and Marrow Registry (ABMTR), all patients' disease status at transplant will be determined prior to initiation of protocol therapy.

For purposes of analysis, patients will be stratified into groups (low (standard) and high-risk for recurrence), since accrual of patients to some of the individual disease/status strata will be slow. The assignment of risk is as follows:

Hodgkin Lymphoma (HL) patients

Hahn, et al., proposed a prognostic score for HL patients undergoing autologous or allogeneic BMT (Hahn et al, 2005). An objective of this protocol is to validate this prognostic model. The following factors will be collected when available:

Standard risk: 0-1 Risk Factors (chemotherapy-resistant disease, KPS <90 and $\geq$ 3 chemotherapy regimens)

High risk: 2-3 Risk Factors (chemotherapy-resistant disease, KPS <90 and $\geq$ 3 chemotherapy regimens)

Non-Hodgkin Lymphoma (NHL) patients

There are no pre-transplant prognostic or risk models for NHL. The

International Prognostic Index (IPI) is a validated prognostic model but uses factors measured at diagnosis. Since patients are referred from multiple non-RPCI physicians, there is inconsistency in the completeness of collecting and reporting these diagnostic factors. For this protocol, the IPI factors will be measured at time of BMT to determine in an exploratory manner if the IPI at BMT is predictive of post-transplant PFS. In addition, we will examine other pre-transplant variables to determine if a prognostic model can be developed. The IPI definitions are located in Appendix I (The International Non-Hodgkin's Lymphoma Prognostic Factors Project). These factors will be collected when available:

International Prognostic Index (All Patients)

Low Risk	0-1 risk factors
Low Intermediate	2 risk factors
High Intermediate	3 risk factors
High	4 or 5 risk factors

International Prognostic Index (≤ 60 years of age)

Low	0 risk factors
Low intermediate	1 risk factor
High intermediate	2 risk factors
High	3 risk factors

Multiple Myeloma patients

There are three risk groups defined by the International Staging System (Greipp et al) as follows. The following factors will be collected when available:

Standard risk:	Stage I, Serum β2M < 3.5 mg/L and serum albumin ≥ 3.5 g/dL (med. survival, 62 months);
Intermediate risk:	Stage II, neither stage I nor III (median survival, 44 months)
High risk:	Stage III, Serum β2M ≥ 5.5 mg/L (median survival, 29 months).

Acute Leukemia patients

A study objective for acute leukemia is to identify which one or more of the below-mentioned individual prognostic factors are the most predictive of PFS. In addition, delineation between a standard and high risk group will be attempted based on a prognostic score using the below-mentioned factors. The following factors will be collected when available:

Prognostic Factors for adult (≥18 years) ALL:

WBC >30,000/ml
Non-T-cell phenotype
t (9;22), t(4;11), t(1;19), t(8;14), trisomy 8, monosomy 7, hypodiploid karyotype
>1 course (4 weeks) to achieve first CR
Age >35 years

Prognostic Factors for pediatric (<18 years) ALL:

Age >10 years
T(9;22), t(4;11), t(8;14)
>12 weeks to achieve 1st CR

Prognostic Factors for pediatric and adult AML:

Antecedenct MDS
Therapy-related AML
FAB M0, 1, 5, 6, 7
WBC>100,000/L at diagnosis
>one course (4 weeks) to achieve first CR
Age>60 years
Complex karyotype abnormalities (monosomy 5, monosomy 7, 3q-, t(10;11)
Flt-3 positive mutation

Amyloidosis, primary or previously treated

All amyloidosis patients will be grouped in the standard risk patient group and analyzed with the MM patients.

Solid Tumor patients

All solid tumor patients will be considered high risk and analyzed for toxicity and overall survival.

5.0 ELIGIBILITY

5.1 Disease Diagnoses: Histologically confirmed diagnosis of malignant hematologic disorders, Amyloidosis or solid tumor malignancy.

5.1.1 Recurrent or Refractory Disease or Disease at High Risk for Recurrence

5.1.1.1 Hodgkin Disease: Relapsed or refractory disease after chemotherapy with a minimum of one standard regimen

5.1.1.2 Non-Hodgkin Lymphoma: (Low, Intermediate or High Grade) Relapsed or refractory disease after chemotherapy with at least one standard regimen or first CR lymphoblastic or small, non-cleaved cell lymphoma at high risk of relapse by high International Prognostic Index (IPI) Score

5.1.1.3 Acute Myeloid Leukemia: Low or High Risk disease in first or second CR or greater in patients in whom the risks of an allogeneic transplant outweigh the benefits.

5.1.1.4 Acute Lymphoblastic Leukemia: Low or High Risk disease in first or second CR in whom the risks of an allogeneic transplant outweigh the benefits.

5.1.1.5 Multiple Myeloma: Low or High Risk in first or greater response (Stable disease or better) or for responding patients at first progression.

5.1.1.6 Other Malignant Lymphoproliferative Disorders: (CLL, Waldenstrom's macroglobulinemia, relapsed or refractory disease after first-line chemotherapy

5.1.1.7 Amyloidosis: primary or previously treated

5.1.1.8 Solid Tumors: Testicular cancer patients who have relapsed disease or primary progressive disease which is responding to salvage therapy; relapsed or advanced-stage newly diagnosed neuroblastoma or small round blue cell tumors in patients ≤ 30 years of age; other patients with solid tumors who have recurred following conventional treatment or are at high risk for relapse, and demonstrate chemosensitivity.

5.1.1.9 Patients with malignancies who would be treated with an autologous stem cell transplant but have a syngeneic donor. A snyngeneic donor would be considered to have the same risk as an autologous stem cell transplant patient.

5.2. Other Criteria

5.2.1. **Performance status 0-2** (Karnofsky ≥70%).
Patients with amyloidosis or MM with decreased KPS due to disease are eligible.

5.2.2. **Age ≥4**

5.2.3. **Life expectancy** >2 months

5.2.4. **Required initial laboratory data**

1. Pulmonary function tests; DLCO or DLVA ≥50% predicted; DLCO to be corrected for hemoglobin and/or alveolar ventilation.
2. Cardiac ventricular ejection fraction ≥50% by radionuclide ventriculogram or echocardiogram.
3. Bilirubin, Alkaline phosphatase, SGOT < 3 x normal.
4. Calculated creatinine clearance < 40 cc/min by the modified Cockroft-Gault formula for adults or the Schwartz formula for pediatrics. (Reference Appendix XII.)
5. Glomerular filtration rate by renal scan for NBL patients, to determine dosing parameters.
6. Positive CMV IgM and/or positive hepatitis serologies demonstrating infection will require an Infectious Disease consult and subsequent clearance.
7. Any active infection will require an Infectious Disease consult and subsequent clearance
8. Peripheral Blood Counts of PMN >1500/μL, and Plt >75,000/μL.
9. Prior to stem cell storage:
   - No radiation within three weeks before stem cell harvest
   - Bone marrow may be used in conjunction with blood progenitor cells
10. Hematologic Malignancy patients with HIV positivity but on appropriate anti-retroviral therapy may go autotransplant with the following laboratory tests. (CD4+ cell count > 75 cells per microliter and HIV copy number < 100,000 per microliter and with Infectious Disease clearance.
11. Acute Leukemia, HL, NHL, MM and Solid Tumor patients must have received 2 cycles of chemotherapy followed by disease-specific restaging prior to mobilization and collection of stem cells. Small round blue cell tumor patients must have received either standard therapy or surgical intervention. The disease status and response to therapy must be known prior to transplant to establish the disease status at transplant. Amyloidosis patients may proceed to BMT without receiving chemotherapy. Please see Appendices in Section 15 for disease-specific restaging criteria and for definitions of disease status at transplant.

5.2.5. **No serious organ dysfunction** unless it is caused by the underlying disease, exclusion criteria include the following:

1. Uncontrolled or severe cardiovascular disease, including recent (<6 months) myocardial infarction, congestive heart failure, symptomatic angina, life-threatening arrhythmia or hypertension
2. Active bacterial, viral, or fungal infection
3. Active peptic ulcer disease
4. Uncontrolled diabetes mellitus

5.2.6. **No serious medical or psychiatric illness; not pregnant**

1. No psychiatric conditions which would prevent delivery of care. Psychology clearance is necessary.

5.2.7. **Allogeneic BMT not possible, or not desirable**

1. Age >65 years
2. No compatible donor identified
3. Estimated risk of graft vs. host disease complications greater than risk of recurrence after autologous BMT

5.2.8. **Adequate bone marrow or blood stem cell dose obtained**

For blood stem cells: total CD 34+ = $\geq$ $2x10^6$/kg or if unable to collect this dose, a total nucleated cell bone marrow dose of $\geq$ $1x10^8$/kg.

5.3 **Registration**:

To register a patient, contact the research nurse/transplant coordinator. Transplant regimens will be assigned as per protocol guidelines by the BMT team. For purposes of reporting to the Autologous Blood and Marrow Registry (ABMTR), all patients' disease status at transplant will be determined prior to initiation of protocol therapy.

5.4 **Data:**

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

6.0 CONSENT FORM

Patients must be aware of the nature of their disease and willingly consent after being informed of the procedure to be followed, the nature of the therapy, alternatives, potential benefits, side-effects, risks and discomforts. There must be no other serious medical or psychiatric illness that would prevent informed consent.

7.0 STRATIFICATION AND RANDOMIZATION

There is no randomization or stratification schema for this protocol. Patients will be assigned treatment (high dose therapy regimen) based on diagnosis, age and co-morbidities

There is no *a priori* stratification of patients at time of registration to determine treatment (high dose therapy regimen), except for the patient's disease (as outlined in section 3.0 Study schema). Patients will be retrospectively stratified based on available data into standard and high risk groups (as defined in section 5.0 Study purposes and objectives) to analyze their impact on long-term PFS.

8.0 TREATMENT PLAN

8.1. **Chemotherapy**: Testicular Cancer, HL, NHL patients must have received 2 cycles of salvage chemotherapy followed by disease-specific restaging prior to mobilization and collection of stem cells. Acute Leukemia and Neuroblastoma patients must have received at least induction therapy and mobilization chemotherapy as consolidation prior to stem cell collection. Small round blue cell tumor patients must have received either surgical treatment or standard chemotherapy. MM patients must have received at least 1 cycle of standard induction therapy. Solid tumor patients must have received at least 2 cycles of chemotherapy before mobilization and stem cell collection. Amyloidosis patients may proceed to BMT without induction chemotherapy. The disease status and response to therapy if applicable must be known prior to transplant to establish the disease status at transplant. Please see Appendices in Section 15 for disease-specific restaging criteria and for definitions of disease status at transplant. Etoposide Phosphate may be substituted for Etoposide in the event of anaphylaxis to Etoposide.

8.2. **Involved-field radiation therapy:** For all patients for whom post-BMT radiation therapy is planned, in the absence of disease progression, radiation should begin no sooner than 4 weeks after transplant. It is recommended that patients with adequate count recovery (PMN >1500/μL, and Plt >75,000/μL.)

8.3 **HIV positive patients:** For all patients with controlled HIV infections, CMV screening should be performed weekly up count recovery until day 100 following transplant. Anti-retroviral therapy should be stopped during chemotherapy and restarted after high dose therapy is completed. Zidovudine should not be used due to myelosuppressive effects. Ritonavir should not be used simultaneously with etoposide which is metabolized by the CYP3A4 pathway. An infectious disease consult should be obtained as part of the transplant workup.

8.4 **Stem Cell Infusion: Day 0** is the day on which the stem cells are infused. As required by scheduling, the stem cells may be infused on the same day after the last fraction of TBI is given.

The procedure of infusing stem cell products may be performed by a trained nurse under the direct supervision of a BMT physician or Nurse Practitioner/Physician Assistant. The stem cells are to remain sterile throughout the infusion process. All patients require continuous pulse oximetry monitoring during the procedure, with oxygen equipment available in the patient's room. All patients will have vital signs recorded before the procedure and at timed intervals during and after stem cell infusion. Emergency drugs, such as diphenhydramine, epinephrine, and corticosteroids will be available for use in appropriate doses. No other blood products should be given electively on the day of transplant, especially within 8 hours of planned infusion time. Patients will be pre-medicated with the following medications:

1) Diphenhydramine 25-50 mg IV, 30 minutes prior to infusion of stem cells.(Pediatric patients will receive Diphenhydramine 1-1.25 mg/kg IV 30 minutes prior to infusion of stem cells with a maximum dose of 50 mg)

2) Hydrocortisone 50 mg IV, 30 minutes prior to infusion of stem cells. (Pediatric patients will receive Hydrocortisone 1 mg/kg IV 30 minutes prior to infusion of stem cells with a maximum dose of 50 mg)

8.5 **Transplant Regimens**

Ideal body weight calculations for all regimens where applicable should be obtained from Appendix II;

Cyclophosphamide (C), BCNU (B), VP-16 (V) (CBV) Summary:

Day	-8	-7	-6	-5	-4	-3	-2	-1	0
Etoposide 2400 mg/ m^2 (34 hr infusion)	X								
Cyclophosphamide1800 mg/ m^2 IV over 2 hrs daily x 4 days (total 7200 mg/ m^2)		X	X	X	X				
BCNU 600 mg/ m^2						X			
Stem Cell Infusion									X

VP-16 (Etoposide) (V) 2400 mg/ m^2 (***actual body weight***) is given by a 34 hr continuous IV

infusion (70 mg/ m^2/hr) beginning on day -8 at 0900 hour hrs and ending on day -7 on at 1900 hours. The undiluted VP-16 will be prepared per pharmacy to infuse with normal saline. The infusion time will be over 34 hrs). During VP-16 infusion, other IV fluids should be kept to a minimum and blood products should not be given except in an emergency. Etoposide Phosphate may be substituted for Etoposide in the event of anaphylaxis to Etoposide.

Cyclophosphamide (C)1800 mg/ m^2 (***ideal body weight or actual body weight, whichever is less***) in 500ml Dextrose 5% Water or Normal Saline, is given by 2 hr IV infusion (1930 - 2130 hrs) days -7, -6, -5, and -4 (total dose 7200 mg/ m^2). **Diphenhydramine** 25-50 mg IV should be given 30 minutes prior to the administration of all Cyclophosphamide doses. When VP-16 infusion is completed, begin IV hydration with D5 1/2 Normal Saline, 1/2 Normal Saline or Normal Saline alone or with 10 mEq Potassium Chloride/L at 150 ml/ m^2/hr. Furosemide, 10-20 mg IV, will be given 2 hrs after each cyclophosphamide dose and then every 4 hrs. as needed to maintain urine output such that Fluids out (O) are at least equal to Fluids in (I). Thus, O should be equal or greater than I once Cyclophosphamide is started.

BCNU (Carmustine) (B). 600 mg/ m^2 (***actual body weight***) in 500 ml Dextrose 5% Water is given by 2 hr IV infusion (1930-2130 hrs), day -3. **Hydrocortisone,** 50 mg IV should be given 30 minutes prior to the administration of the BCNU dose. Hyperhydration is continued until 24 hrs. after the BCNU dose (day -2).

Melphalan 200 (M200) Summary:

Day	-2	-1	0
Melphalan 200 mg/ m^2 for myeloma and amyloidosis patients	X		
Stem Cell Infusion			X

Melphalan (M200). 200 mg/ m^2 (***actual body weight***) in diluent provided by manufacturer to a final concentration of 5 mg/ml to infuse over 30 minutes, starting between 1800 and 2100 hrs on day -2. A minimum of 4 hours prior to first dose, begin IV hydration. Hyperhydration is continued until 24 hrs. after the melphalan dose. A minimum of 4 weeks must pass before a second melphalan 200 mg/ m^2 dose is given for those patients who receive a second transplant.

Melphalan 120 (M120) Summary to be used for patients not eligible for Melphalan 200 due to inadequate renal, cardiac, or other organ function or decreased KPS due to disease:

Day	-2	-1	0
Melphalan 120mg/ m^2 for amyloidosis, or multiple myeloma if indicated	X		
Stem Cell Infusion			X

Melphalan (M120). 120 mg/ m^2 (***actual body weight***) in diluent provided by manufacturer to a final concentration of 5 mg/ml to infuse over 30 minutes, starting between 1800 and 2100 hrs on day -2. A minimum of 4 hours prior to first dose, begin IV hydration. Hyperhydration is continued until 24 hrs. after the melphalan dose. A minimum of 4 weeks must pass before a second melphalan 120 mg/ m^2 dose is given for those patients who receive a second transplant.

Busulfan(B), Cyclophosphamide(C) (Bu/C2iv) summary:

Day	-8	-7	-6	-5	-4	-3	-2	-1	0
Adult patients: levetiracetam 500 mg PO or IV twice daily Pediatric patients: levetiracetam 10 mg/kg PO or IV (max 500 mg/dose) twice daily.	X								
Adult patients: Levetiracetam 500 mg PO or IV twice daily Pediatric patients: levetiracetam 10 mg/kg PO or IV (max 500 mg/dose) twice daily.		X	X	X	X	X			
Busulfan (IV) 0.8mg/kg q6h **for** 4 days (total 12.8 mg/kg		X	X	X	X				
Cyclophosphamide 60 mg/kg IV over 2 hours daily x 2 days (total 120 mg/kg)						X	X		
Stem Cell Infusion									X

Patients receiving this regimen cannot start busulfan on a Friday or have levels drawn the day before a holiday unless the ideal body weight dose is used. Busulfan levels are used to

adjust dose in those receiving busulfan based on an adjusted body weight.

All patients receiving busulfan must receive seizure prophylaxis:

Adults: Levetiracetam: 500 mg IV or PO twice daily to start on Day -8 and to continue until 24 hours after busulfan is finished.

Pediatrics: levetiracetam 10 mg/kg IV or PO (max 500mg/dose) IV or PO twice daily to start on Day -8 and to continue until 24 hours after busulfan is finished.

Busulfan (Bu). 0.8mg/kg ***adjusted body weight for obese patients*** should be used and busulfan levels must be obtained unless not available. If ideal body weight is greater than actual body weight, use actual body weight. At 0900 hrs on day -7 begin busulfan over 2 hours IV, then every 6h for 16 total doses (total dose 12.8 mg/kg). Hyperhydration is not required. At the initiation of the first dose of busulfan begin IV hydration with D5 1/2 Normal Saline, 1/2 Normal Saline or Normal Saline alone or with 10 mEq Potassium Chloride/L at 50 ml/ m^2/hr.

Pharmacy will calculate volume of Normal Saline or Dextrose 5%Water for the 2 hour infusion.

Busulfan levels are to be drawn at least 4 time points: 1) One hundred and fifteen (115) minutes after start of infusion, 2) Two and one half (2.5) hours after start of infusion, 3) Four (4) hours after the start of infusion and 4) Six (6) hours after the start of the infusion (before the start of the 2nd dose).

If levels cannot be obtained, the busulfan will be dosed as follows:

Busulfan (Bu). 0.8mg/kg ***ideal body weight (IBW) or actual body weight whichever is less*** will be used. At 0900 hrs on day -7 begin busulfan over 2 hours IV then every 6h for 16 total doses (total dose 12.8 mg/kg).

Pharmacy will calculate volume of Normal Saline or Dextrose 5%Water for the 2 hour infusion.

Cyclophosphamide (C). Cyclophosphamide, 60 mg/kg ***(ideal body weight or actual body weight whichever is less)***, in 500ml Normal Saline is given by 2 hr IV infusion (1100 -1300 hrs) days -3, and -2 (total dose 120 mg/kg). **Diphenhydramine** 25-50 mg IV should be given 30 minutes prior to the administration of all Cyclophosphamide doses. Four hours prior to the first dose of Cyclophosphamide, begin IV hydration at 150 ml/ m^2/hr.

Furosemide, 10-20 mg IV, will be given 2 hrs after each cyclophosphamide dose and then every 4 hrs. as needed to maintain urine output such that Fluids out (O) are at least equal to Fluids in (I).

Thus, O should be equal or greater than I once Cyclophosphamide is started.

Cyclophosphamide (C), TBI (CT6) Summary:

Day	-5	-4	-3	-2	-1*	0*
C 60 mg/kg	X	X				
T 200 cGy (total 1200 cGy)			X/X	X/X	X/X	
Stem Cell Infusion*						X

Cyclophosphamide (C). Cyclophosphamide, 60 mg/kg ***(ideal body weight or actual body weight whichever is less)***, in 500ml Normal Saline is given by 2 hr IV infusion (1100 -1300 hrs) days -4 and – 5 (total dose 120 mg/kg). **Diphenhydramine** 25-50 mg IV should be given 30 minutes prior to the administration of all Cyclophosphamide doses. Four hours prior to the first dose of Cyclophosphamide, begin IV hydration at 150 ml/ m^2/hr. Furosemide, 10-20 mg IV, will be given 2 hrs after each cyclophosphamide dose and then every 4 hrs. as needed to maintain urine output such that Fluids out (O) are at least equal to Fluids in (I). Thus, O should be equal or greater than I once Cyclophosphamide is started.

Total Body Irradiation (T). 200 cGy twice daily will be given over 3 days (minimum 6 hrs between fractions) at a dose rate of 5-25 cGy/min. Total dose 1200 cGy in 6 fractions over 3 days, with lung shielding. See Appendix III

*As required by scheduling, the stem cells may be infused on the same day after the last fraction of TBI is given.

Cyclophosphamide(C), Carboplatin Cp), Thiotepa(Tt) (CTtCp) summary:

Day:	-7	-6	-5	-4	-3	-2	-1	0
Cyclophosphamide 1500 mg/ m^{2*}/day (total 6000 mg/m^2)	X	X	X	X				
Carboplatin 200 mg/ m^{2*}/day (total 800 mg/m^2)	X	X	X	X				
Thiotepa 125mg/ m^{2*}/day (total 500 mg/m^2)	X	X	X	X				
Mesna 1500 mg/ m^{2*}/day (total 7500 mg/m^2)	X	X	X	X	X			
Stem Cell Infusion								X

*** Please note: To determine weight for m^2 calculation for <u>all four drugs</u> in this regimen, use the average of the patient's actual and ideal body weights *unless actual weight is less than ideal body weight, then use actual body weight***

Cyclophosphamide (C) 1500 mg/ m^2/day ***(average of the actual and ideal body weights) -*** on days -7, -6, -5, -4 for a total dose of 6000 mg/ m^2 total dose.. **Diphenhydramine** 25-50 mg IV should be given 30 minutes prior to the administration of all Cyclophosphamide doses. Dilute cyclophosphamide in Normal Saline to a final volume of 1,000 ml and infuse over 24 hours.

Carboplatin (Cp) 200 mg/ m^2 /day ***(average of the actual and ideal body weights)*** on days -7, -6, -5, -4 for a total dose of 800 mg/ m^2total dose Dilute carboplatin in Dextrose 5% Water to final volume of 500 ml and infuse over 24 hours. Begin infusion to coincide with cyclophosphamide infusion, and infuse through a separate lumen. Carboplatin solutions should not be prepared or administered with needles or IV administration sets containing aluminum parts that might come in contact with the drug.

Thiotepa (Tt) 125mg/ m^2 /day ***(average of the actual and ideal body weights)*** days -7, -6, -5, -4 for a total dose of 500 mg/ m^2 / total dose. Reconstitute each thiotepa 15 mg vial with 1.5 ml sterile water for injection to provide solution containing 10 mg of thiotepa per ml of sterile water. Further dilute solution to 1 mg/ml with 0.9% Sodium Chloride and infuse over 24 hours.

Mesna.
Mesna and cyclophosphamide should be mixed together and infused over days -7, -6, -5, and -4. Mesna alone should then be continued over day -3 until 24 hours after the last cyclophosphamide dose.

VP-16 (V), Carboplatin(Cp) (VCp) summary:

Day	-6	-5	-4	-3	-2	-1	0
Etoposide 750 mg/m^2 IV over 2-3 hrs daily x 3 days/ (total 2250 mg/ m^2)	X	X	X				
Carboplatin 700 mg/m^2/day (total 2100 mg/ m^2)	X	X	X				
Stem cell Infusion							X

VP-16 (Etoposide) (V). 750 mg/ m^2 ***(actual body weight)*** undiluted drug is to run with Normal Saline solution over 2-3 hours, beginning at between 9 and 11 AM, days -6, -5, -4 for a total dose of 2250 mg/ m^2. VP-16 should be given prior to the Carboplatin as the volume of saline with the VP-16 acts as a fluid load for the Carboplatin. Etoposide Phosphate may be substituted for Etoposide in the event of anaphylaxis to Etoposide. It may be run over 2-4 hours.

Carboplatin (Cp) 700 mg/m^2 ***(actual body weight)*** to a final concentration of 0.5 – 2 mg/mL Dextrose 5% Water IV infusion over 30 minutes, within 2 hours of the completion of VP-16, days -6, -5, -4 for a total dose of 2100 mg/ m^2. Carboplatin solutions should not be prepared or administered with needles or IV administration sets containing aluminum parts that might come in contact with the drug.

Thiotepa(Tt), Cyclophosphamide(C), Mesna (TtC1500) Summary:

(Please note change in dose for patients less than 12 kg)

(**Transplant #1:)**

Day	-7	-6	-5	-4	-3	-2	-1	0
Tt 300mg/m^2/day (total 900 mg/m^2)	X	X	X*					
C 1500 mg/m^2/day (total 6000 mg/m^2)**			X	X	X	X		
Mesna 300 mg/m^2/dose** x 4 doses/day			x/x/x/x	x/x/x/x	x/x/x/x	x/x/x/x		
Stem Cell Infusion								X

* Start early enough on Day -5 to give dose prior to cyclophosphamide

** Initial dose of mesna added to cyclophosphamide bag, then doses at 3, 6 and 9 hours should be added to 50 ml D5W and infused over 15 minutes.

If patient's weight is less than 12 kg:
Thiotepa: 10 mg/kg/day
Cyclophosphamide : 50 mg/kg/day
Mesna: 10 mg/kg/dose x 4 doses as above

Thiotepa (T) 300mg/m^2 ***(actual body weight)*** at a concentration of 1 mg per ml in NS to infuse over 2 hrs, starting between 0900 and1100 on days -7, day-6, and day-5 at a total dose 900 mg/m^2. A minimum of 12 hours prior to first dose, begin IV hydration per standard of care.

Cyclophosphamide (C) 1500 mg/m^2 ***(ideal body weight or actual body weight whichever is less)*** 500ml Normal Saline is given by 2 hr IV infusion for adults or for pediatric patients; 100 ml per m^2 NS is given by 1 hour IV infusion days -5, -4, -3 and -2 for a total dose of 6000 mg /m^2. **Diphenhydramine** 1 mg/kg (maximum dose 25 mg) IV should be given 30 minutes prior to the administration of all Cyclophosphamide doses. .

Mesna: The initial dose of Mesna, 300 mg/m^2 **(actual body weight)** is mixed in the same bag with the Cyclophosphamide and infused over 2 hours. The three subsequent doses of Mesna 300 mg/m^2 are mixed in 50 cc of D5W and infused at 200 ml/hr (over 15 minutes).

Note: Urine output should be maintained at 2 cc/kg/hr averaged over 2 hours for 24 hours following Cyclophosphamide administration for pediatric patients. If urine output falls below this parameter, give Furosemide 0.5 mg/kg IV (maximum dose 20 mg). For adult patients, maintain urine output such that Fluids out (O) are at least equal to Fluids in (I). Thus, O should be equal or greater than I once Cyclophosphamide is started. When the urine output falls below the above parameters, , call the clinical team.

Carboplatin(Cp), Etoposide (E), Melphalan (M) (ECpM) Summary:

(Please note change in dose for patient less than 12 kg and for adults 18-30 years old)

(Transplant #2)

- If pediatric patient and GFR is **greater** than 100 ml/min/1.73m^2

Day	-7	-6	-5	-4	-3	-2	-1	0
Carboplatin 375 mg/ m^2/day, CIVI (total 1500 mg/ m^2)	X	X	X	X				
Etoposide 300 mg/ m^2/day, CIVI (total 1200 mg/ m^2)	X	X	X	X				
Melphalan 60 mg/ m^2/day (total 180 mg/ m^2)	X	X	X					
Stem Cell Infusion								X

If patient's weight is less than 12 kg and GFR>100 ml/min/1.73m^2:
Cp: 12.5 mg/kg/day

E: 10 mg/kg/day
M: 2 mg/kg/day

Carboplatin (Cp) 375 mg/ m^2/day ***(actual body weight)*** CIVI on days -7, -6, -5, -4 at a total 1500 mg/ m^2 if GFR is greater than 100 ml/min/1.73m^2. Carboplatin is given in Dextrose 5% IV infusion (0.5-2.0 mg/ml) over 24 hr CIVI on days -7, -6, -5, and -4. Carboplatin solutions should not be prepared or administered with needles or IV administration sets containing aluminum parts that might come in contact with the drug.

Etoposide (E) 300 mg/ m^2/day ***(actual body weight)*** CIVI on days -7, -6, -5, -4 for a total dose of 1200 mg/ m^2. The undiluted etoposide will be prepared per pharmacy to infuse with normal saline. The infusion will run over 24 hours CIVI. This should be a separate infusion from the carboplatin in NS on these days. Etoposide Phosphate may be substituted for Etoposide in the event of anaphylaxis to Etoposide.

Melphalan (M). 60 mg/m^2 ***(actual body weight)*** in provided diluent at a final concentration of 5 mg/ml to infuse over 30 minutes per day on days -7, -6, 5 for a total dose of 180 mg/m^2.

Hyperhydration is continued until 24 hours after the melphalan dose.

- If pediatric patient and GFR is **less** than 100 ml/min/1.73m^2

Day	-7	-6	-5	-4	-3	-2	-1	0
Carboplatin 4.1 AUC* dose/day, CIVI*	X	X	X	X				
Etoposide 200 mg/ m^2/day, CIV1 (total 800 mg/ m^2)	X	X	X	X				
Melphalan 60 mg/ m^2/day (total 180 mg/ m^2)	X	X	X					
Stem Cell Infusion								X

***AUC** dose is the Absolute Carboplatin dose **(NOT** per m2 or per kg**).**
(See Appendix 2 for calculation)

If patient's weight is less than 12 kg and GFR<100 ml/min/1.73m^2:
Carbo: AUC of 4.1
Etoposide: 6.7 mg/kg/day
Melphalan: 2 mg/kg/day

Carboplatin (Cp) The dose is 4.1 AUC if the GFR is less than 100 ml/min/1.73m^2. Carboplatin is given in Dextrose 5% IV infusion (0.5-2.0 mg/ml) over 24 hr CIVI on days -7, -6, -5, and -4. Carboplatin solutions should not be prepared or administered with needles or IV administration sets containing aluminum parts that might come in contact with the drug.

Etoposide (E) 200 mg/ m^2/day ***(actual body weight)*** CIVI on days -7, -6, -5, -4 for a total

dose of 800 mg/ m^2. The undiluted etoposide will be prepared per pharmacy to infuse with normal saline. The infusion time will be over run over 24 hours CIVI. This should be a separate infusion from the carboplatin on these days. Etoposide Phosphate may be substituted for Etoposide in the event of anaphylaxis to Etoposide.

Melphalan (M). 60 mg/m^2 ***(actual body weight)*** in provided diluent at a final concentration of 5 mg/ml to infuse over 30 minutes per day on days -7, -6, 5 for a total dose of 180 mg/m^2.

Hyperhydration is continued until 24 hours after the melphalan dose.

- If Patient is 18 to 30 years of age

Day	-7	-6	-5	-4	-3	-2	-1	0
Carboplatin 4.1 AUC* dose/day, CIVI*	X	X	X	X				
Etoposide 300 mg/ m^2/day, CIV1 (total 1200 mg/ m^2)	X	X	X	X				
Melphalan 60 mg/ m^2/day (total 180 mg/ m^2)	X	X	X					
Stem Cell Infusion								X

***AUC** dose is the Absolute Carboplatin dose **(NOT** per m2 or per kg**).** (See Appendix 2 for calculations)

Carboplatin (Cp) The Carboplatin dose is based on an AUC of 4.1 using the Calvert Formula in Appendix 2. The Creatinine Clearance will be based on a 24 hour creatinine clearance or Cockroft Gault formula (Appendix 2). Carboplatin is given in Dextrose 5% IV infusion (0.5-2.0 mg/ml) over 24 hr CIVI on days -7, -6, -5, and -4. Carboplatin solutions should not be prepared or administered with needles or IV administration sets containing aluminum parts that might come in contact with the drug.

Etoposide (E) 300 mg/ m^2/day ***(actual body weight)*** CIVI on days -7, -6, -5, -4 for a total dose of 1200 mg/ m^2. The undiluted etoposide will be prepared per pharmacy to infuse with normal saline. The infusion will run over 24 hours CIVI This should be a separate infusion from the carboplatin on these days. Etoposide Phosphate may be substituted for Etoposide in the event of anaphylaxis to Etoposide.

Melphalan (M). 60 mg/m^2 ***(actual body weight)*** in provided diluent at a final concentration of 5 mg/ml to infuse over 30 minutes per day on days -7, -6, 5 for a total dose of 180 mg/m^2.

Hyperhydration is continued until 24 hours after the melphalan dose.

REQUIRED DATA / Study Calendar

1. Important hematologic recovery endpoints
   day PMN >500/µL, >1000/µL; Plt >25K, >100K; Hb >10gm%
   day of last Plt transfusion, last RBC transfusion
2. Day(s) of occurrence of severe toxicity (gr3)

Tests/Observations	Pre-Rx	Post-Rx***	Post-Disch
Signed Consent Form	X	--	--
Ht / Wt / BSA	X	--	--
Ideal Body Wt / Adjusted Body Wt (if applicable)	X	--	--
Serology (Infectious disease Screening)	X	--	--
Cr Clearance	X	--	--
PFTs / DLCO / DLVA	X	--	--
MUGA or ECHO	X	--	--
Ekg	X	--	--
Quantitative Ig's	X	--	--
BM aspirate, biopsy*	X	d +100 for any not in marrow remission prior to transplant as clinically indicated.	
Staging Profile**	X	Repeat positive studies d +100 and d+360; then as clinically indicated.	
CBC	X	q day to PMN > 500, Plt > 20K, then as clinically indicated	
Urinalysis (biochemical)	X	As clinically indicated	--
PT-INR	X	As clinically indicated	--
Full Chemistry Panel (Complete Metabolic Panel)	X		As clinically indicated
Chest X-ray	X	As clinically indicated --	
Performance Status	X	qwk	As clinically indicated
Toxicity (Bearman and CTC)	--	Weekly	q l mo until nl

FLOW CYTOMETRY
Quantitative IGs day 100, 180, 360

§ d 0 is day of stem cell transplant; studies to be obtained as close to indicated time as possible.
* If evidence of disease at any time prior to BMT. Obtain cytogenetics if previously abnormal.
** For pts. with HL/NHL lymphoma: Non-invasive studies including: (1) measurement (perpendicular diameters) of palpable disease, (2) CT scan of chest, abdomen, pelvis, (3) Whole-body Gallium or PET scan.
For pts. with testicular cancer: AFP and/or beta HCG Pretransplant and at d +100
For pts. with neuroblastoma: HVA and VMA Pretransplant and 30 days after 2nd transplant; Also, CT and bone scans and skeletal survey 30 days after 2nd transplant.
*** Post therapy is defined as until engraftment and /or discharge from hospital.

Intervals shown are the minimum requirement

9.0 CRITERIA FOR RESPONSE AND PROGRESSION

Response definitions for each disease are defined in the Appendices (Section 15.)

10.0 INFORMATION ON DRUG FORMULATION AND AVAILABILITY:

10.1 **Etoposide** (VP-16) is commercially available in vials containing 20 mg/ml of etoposide Drug is stable at room temperature. The etoposide should be transferred to non-PVC (DHEP free) bags which is chemically stable for 48 hours at room temperature. Do not administer cloudy or precipitated drug.

10.2 **Cyclophosphamide** (Cytoxan) is commercially available in 500, 1000 mg, and 2000 mg vials. Dilute with 25, 50, or 100 ml, respectively, of 0.9% sodium chloride yielding a concentration of 20 mg/ml which is stable for 24 hours at room temperature. Further dilute with 0.9% sodium chloride.

10.3 **BCNU** (carmustine) is commercially available in 100 mg vials of lyophylized drug which is stable for 2 years when stored refrigerated. Immediately prior to intravenous administration, dissolve contents of vial in 1 ml of supplied diluent (absolute alcohol) and add 9 ml of Sterile Water for Injection, U.S.P. for a concentration of 10 mg/mL. The dose of BCNU should be diluted further with 5% Dextrose Injection, U.S.P. to final concentration dose mg/mL in 500mL in a glass container and protected from light. Product is only stable for 8 hours after reconstitution.

10.4 **Melphalan** is commercially available in 50 mg vials. It is to be admixed just prior to intravenous administration and is stable for 90 min. at 5 mg/mL. The dose of melphalan will be diluted with diluent provided to a final concentration of 5 mg/ml and protected from light.

10.5 **Busulfan** is commercially available in 60 mg/10 ml (6 mg/ml) single-use ampules. IV busulfan should be diluted with 0.9% NaCl or 5% Dextrose Injection, U.S.P. The diluent quantity should be 10 times the volume of busulfan, ensuring that the final concentration of busulfan is approximately >0.5 mg/ml. Mixed solution is stable for 8 hours at room temperature (25° C), but the infusion must be completed within that time. Busulfan diluted in 0.9% NaCl is stable under refrigeration (2-8° C) for up to 12 hours, but the infusion must be completed within that time.

10.6 **Thiotepa** is commercially available as a lyophilized powder in 15 mg vials. After reconstitution with 1.5 ml Sterile Water for Injection, the resulting solution is stable for 8 hours. It must be diluted further with D5W or NS for IV infusion. A 0.22 micron filter recommended (see package insert).

10.7 **Carboplatin** is commercially available in vials of 50 mg/5 ml, 150 mg/15 ml, 450 mg/45 ml, and 600 mg/60 ml aqueous solutions. A further dilution of up to 20-fold with 0.9% Sodium Chloride Injection, U.S.P. or 5% dextrose in water can be made (final concentration >0.5 mg/ ml). Do not use aluminum needles for preparation or administration of drug. Unopened vials can be stored at room temperature in the dark.

POTENTIAL TOXICITY - MANAGEMENT AND DOSE MODIFICATIONS

Toxicity Grading: The Bearman Toxicity Criteria will be used for the grading and reporting of all toxicities. (See Appendix IV). Grade 4 hematosuppression does not have to be reported for agents known and expected to cause hematosuppression at the dose used.

Hematologic: Three to four weeks of severe pancytopenia (PMN < 500/µL, Platelets < 20,000/µL) are expected, and rarely patients may fail to engraft. Despite optimal antibiotics, 5% of patients treated with intensive chemotherapy may die as a result of infection. Infection prophylaxis and treatment will be given according to standard accepted medical practice. With prophylactic platelet transfusions, the risk of death from hemorrhage is <5%. Use of purged marrow may delay recovery and increase the risk of graft failure to as much as 5%.

Hepatic: Moderate toxicity is common. More severe, possibly fatal, liver toxicity can occur, usually in the form of veno-occlusive disease. With the study regimens the incidence of fatal liver toxicity should be < 5%. Management of liver toxicity is with standard supportive and symptomatic measures. Avoid exposure of patients to other hepatotoxic agents whenever possible.

Pulmonary: Idiopathic interstitial pneumonitis (IP) is possible after high dose alkylating agent therapy or TBI. With the study regimens the risk of fatal idiopathic IP is felt to be < 5%. Patients with diffuse pulmonary infiltrates often present a difficult diagnostic and management problem. Whenever possible, histologic confirmation of the diagnosis should be attempted by bronchoalveoar lavage, or transbronchial or open-lung biopsy to exclude infectious causes, including cytomegalovirus.

Cardiac: High-dose cyclophosphamide can produce fatal hemorrhagic pancarditis. The risk of fatal cardiac toxicity with the study regimens is <5%. Patients who develop signs of congestive heart failure not attributable to fluid overload should be evaluated for signs of carditis before additional CPA is given. Studies should include ECG (to compare voltage to pretreatment ECG), radionuclide ventriculogram, and/or echocardiography. If evidence of pericarditis, pericardial effusion or impaired myocardial function (decreased ejection fraction) is found, no further chemotherapy will be administered. In this situation patients must be watched carefully for signs of pericardial tamponade; pericardiectomy may be required.

CNS:

Busulfan, in high doses, can cause grand mal seizures. Patients will be treated prophylactically with phenytoin to minimize the risk of busulfan-induced seizures.

Thiotepa can cause temporary confusion, loss of memory, and inappropriate behavior lasting several days. In severe cases the damage may not be reversible. One severe case has occurred in a patient at RPCI with the thiotepa dose used in the current study. The patient

had undergone surgical resection of a metastatic lesion and whole brain irradiation prior to thiotepa treatment.

Some antibiotics, which may be needed to treat infections during the period of low white blood cell counts, can cause VIIIth nerve damage resulting in hearing loss (especially high-frequency tones) and dizziness which may be permanent. To minimize this possibility, antibiotic levels will be monitored.

Genitourinary: Urinary metabolites of cyclophosphamide can produce hemorrhagic cystitis. Microscopic hematuria is common following high dose CPA regimens and up to 20% of patients may have gross hematuria or symptoms. Vigorous hydration of patients (3,000 ml/m2/day) prior to beginning CPA and continuing until 24 hours after the final CPA dose produces a dilute urine and reduces the likelihood of severe cystitis. The risk of life-threatening cystitis is estimated to be <1%. For patients with a history of previous cyclophosphamide induced hemorrhagic cystitis, MESNA may be used.

Busulfan, thiotepa and TBI in the doses employed can cause permanent sterility in all patients.

Renal: Mild renal insufficiency is common in patients given nephrotoxic antibiotics (aminoglycosides and amphotericin B) which are avoided whenever possible. When aminoglycosides must be used, serum levels are closely monitored. Carboplatin in high doses can produce renal toxicity which can be minimized by vigorous hydration and avoidance of concomitant exposure to other nephrotoxic agents.

Gastrointestinal:

Nausea/Vomiting - Many patients will experience moderate to severe toxicity. All patients should receive vigorous antiemetic treatment.

Stomatitis/Dysphagia - Many patients will experience moderate to severe toxicity. Adequate pain relief often requires parenteral narcotics.

Diarrhea - Most patients will experience moderate to severe diarrhea which responds to standard symptomatic therapy. Appropriate studies are needed to exclude infectious causes

of diarrhea, especially C. difficile.

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

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

Allergy: Mild allergic reactions including rash, hives, itching nasal stuffiness, sinus congestion, sneezing, watery eyes, and running nose occur occasionally; more severe reactions with low blood pressure and wheezing are rare.

Risks of marrow donation: The most frequent side effect of marrow donation is pain and stiffness over the hip bones lasting from several days to 1-2 weeks. Blood loss from the procedure results in anemia which may require treatment with iron tablets or with red blood cell transfusions. Infection of the skin, soft tissue, or bone is a rare possibility which could lead to the need for antibiotic treatment. Rarely untoward reactions to anesthesia occur and can be fatal (risk estimated to be 1 in 10,000).

Risks of stem cell collection: The most frequent side effects are dysesthesias from citrate. Other side effects include muscle cramps, infection, and bleeding.

Risks of blood or marrow infusion: For transplantation, the blood or bone marrow is thawed and injected intravenously. Common side effects are transient cough, flushing, nausea and vomiting which may be caused by the chemical (DMSO, dimethylsulfoxide) used to protect the blood or marrow from damage during freezing, or possibly by temporary trapping cellular particles in the lungs. Rarely, severe allergic reaction to DMSO may occur and subsequent stem cell products may require volume reduction.. Hemoglobinuria may be present for several hours due to lysis of RBC's in the marrow damaged by freezing. In rare circumstances, a seizure can occur during the stem cell reinfusion.

In summary, overall transplant related mortality is expected to be approximately 5-10% due to graft failure, regimen-related organ toxicity, infection, and hemorrhage. Risk factors associated with higher transplant related mortality include more prior therapy, poorer performance status, and more intensive transplant regimens.

11.0 REPORTING OF ADVERSE DRUG REACTIONS/ DATA SAFETY MONITORING PLAN

In accordance with the NCI approved RPCI Data Safety Monitoring Plan, this study will conform to the stipulations of that Plan that are summarized below:

Investigator Requirements and Responsibilities

The principal investigator (PI) of this study is ultimately responsible for every aspect of the design, conduct, and final analysis of his protocol. The PI is responsible to insure continuous, close monitoring of subjects enrolled on his clinical trial.

SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effects or precaution. This includes any experience that:

- Results in death.
- Is a life-threatening adverse drug experience.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  For the purpose of this study, hospitalizations for protocol-scheduled procedures, blood product transfusions, or for social reasons (i.e., awaiting transport home) will not be considered SAE's.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Requires medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Serious Adverse Events

All SAEs occurring during the course of the study or within 30 days of the last administration of study procedure must be reported to the Study Chair and Clinical Research Services (CRS) within 24 hours of the knowledge of occurrence (this refers to an AE that meets one or more of the aforementioned serious criteria), CRS will forward the SAE into the IRB. This can be done by faxing a completed SAE Report form (716- 845-3562) or by e-mail description to Dawn Sullivan in CRS. Where the initial report is made verbally or by telephone, a written confirmation within a further 24 hours must follow.

SAE Follow-up

For all SAE's occurring during the study or within 30 days of the last administration of study procedure, the investigator must submit follow-up reports the Study Chair and Clinical Research Services, CRS will notify Institutional Review Board regarding the patient's subsequent course until the SAE has subsided, or until the condition stabilizes, the patient dies, or receives alternative therapy.

Local reporting for data and safety monitoring for the protocol will require SAE's to be reported to the IRB-01 and IRB-03, via the Clinical Research Service Office, using the Adverse Event Reporting form and the FDA MEDWATCH SAE reporting form.

On the anniversary date of the approved protocol at RPCI, the principal investigator will be required to report to the IRB the number of patients entered on the trial, the number of patients treated, a summary of all adverse events reported to date using CTC 3.0 grading and Bearman

(See Appendix X), a specific list of serious adverse events requiring immediate reporting, and significant literature reporting developments that may affect the safety of participants or the ethics of the study.

Reporting of SAEs includes:
1. failure to engraft (defined as a patient alive on day 45 with no ANC recovery)
2. graft failure (defined as a patient who had initial ANC recovery but subsequently had a deceline in ANC that required additional stem cell support).

The IRB will review annual data and safety monitoring reports and make recommendations on whether the study should continue unchanged, require modification/amendment, or be closed based on unacceptable risk to participants.

DATA AND SAFETY MONITORING PLAN

The Principal Investigator (PI) will be responsible for continuous monitoring of the safety of the study. This monitoring is accomplished by the following:

Patient Outcomes Rounds are held weekly on the transplant unit, at which time all BMT patient care is reviewed, including:
- medications (chemotherapy for high dose therapy regimens; graft-versus-host disease prophylactic and therapeutic medications; and possible drug interactions)
- adverse events and/or adverse reactions to any medication, procedure, or other treatment; reports are filed according to RPCI policy and procedure
- regimen-related toxicity, based on Bearman toxicity grading, and/or Common Toxicity Criteria (CTC) if the toxicity does not correlate with a Bearman grade
- a properly signed and dated transplant consent
- compliance issues that could compromise patient safety; pretransplant, a conference is held for all autologous patients for the purpose of describing the need for autologous patients to obtain lodging within a 30 mile radius of the hospital and to have a caregiver present at all times while the patient is an outpatient. In addition, psychosocial evaluations are completed on all high-risk autologous transplant patients prior to transplant, to identify any compliance issues
- other aspects of safety monitoring as prescribed by the BMT Standards of Care and common clinical practice. These include daily physical examinations, clinical laboratory testing, routine surveillance cultures, therapeutic drug level monitoring (i.e., Busulfan, Vancomycin, FK506, Tobramycin, Cyclosporine). Patients who have been discharged from the hospital are monitored in the BMT Clinic until all transplant-related issues are resolved and they are returned to the care of their referring physicians.

The BMT Quality Assurance plan requires quarterly reporting to the BMT Quality Assurance Committee, which in turn reports to the hospital Quality Assurance Committee. Indicators for BMT patient safety monitoring include:
- Patient complaints
- Serious adverse events
- Bearman toxicity grades 3 and 4

- Variances in the delivery of standard care
- Readmissions prior to day +60 post transplant
- Deaths occurring prior to day +100 post transplant
- Engraftment

Followup on all transplant patients is continued even after they have returned to the care of their referring physicians. A Long Term Transplant Clinic has been established, which provides care for autologous patients with chronic complications, as well as assessments to identify dental, bone, and psychosocial complications.

All outcomes are reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) which is a merger of the International Bone Marrow Transplant Registry (IBMTR) the Autologous Bone Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP). Registry reports are reviewed internally prior to submission to the respective registry. These data are also entered into the RPCI BMT Database, from which patient outcomes are assessed and reviewed on a regular basis. Regimen-related toxicities reported in this fashion have resulted in a number of changes to transplant protocols since 1997, thus decreasing toxicity and improving outcomes in a number of patient groups.

Registry reports also establish the efficacy of treatment as measured by overall best response to transplant at day +100 and on subsequent annual reports. The patients' medical records serve as original source documents for all reporting. Audits are conducted every two to three years by the CIBMTR and the Foundation for the Accreditation of Cellular Therapy (FACT).

12.0 STATISTICAL ANALYSIS

12.1. **Study Design**:

This is a pilot study of high dose therapy and autologous blood or marrow transplantation for patients with hematologic malignancies or disorders who have failed low-dose chemotherapy or who are in their first remission, but are at high risk of relapse. Patients will be stratified by 6 disease groups (acute leukemia, HL, NHL, MM/amyloidosis, and solid tumors). All statistical analyses will be performed separately for each disease and regimen and no formal comparisons will be made between regimens.

Design

The primary objective of this multi-arm Pilot is to assess the efficacy of the proposed blood or marrow transplant high dose therapy regimens for NHL, HL, and MM patients through estimation of the progression free survival distribution. Progression free survival is defined as the time from date of transplantation to the date of first observed disease progression or death due to any cause. Patients who are alive and disease free at the last study assessment will be treated as censored. The projected accrual is approximately **3** per month, and therefore recruitment is expected to be complete in **84** months follow the study starting point. The target is 224 but up to 252 patients may

be accrued. Please see the Table below for accrual by disease type. Subjects will be followed for at least 60 months after recruitment completion, so total study duration will be **12** years. The proposed samples sizes for each of the disease/regimen combinations appear in the table below. This is a total of 224 and this population size will allow for estimation of interest. The accrual rate of approximately 3 per month will allow for up to a total accrual of 252 over approximately 84 months. Based on refinement of accrual rate, we were able to decrease the total from 530 to 224. This will still allow for estimation of parameters of interest. These numbers are based on historical enrollment and the results of this exploratory pilot study will be used in the planning of future clinical trials. An exact sample size is not necessary as we need an estimate of accrual. The precision associated with the survival estimates will be approximately the same for a range of pt sample sizes (e.g. 33 versus 37 will approximately be the same as35).

Toxicity: The historical Treatment-Related (TRM) at 100 days has been less than 7% which was the original stopping parameter for this study. As we have enrolled 91 patients receiving 95 transplant since 7/7/06 and have 1 death due to Regimen-Related Toxicity (1%). This is considered acceptable when compared to National Standards (http://www.cibmtr.org/)

Disease (across)	NHL	HL	MM	Amyloid	Acute Leuk	ST
Regimens (below)						
BuCy2iv	35	10			11	
CBV	35	25				
Mel120			20	5		
Mel200			50	9		
CT6					10	
ST Regimens						14
Totals (224)	70	35	70	14	21	14

NHL, Non-Hodgkin Lymphoma; HL, Hodgkin Lymphoma; MM, Multiple Myeloma; Acute Leuk, Acute Leukemia; ST, Solid Tumor; BuCy2iv, Busulfan and Cyclophosphamide; CBV, Cyclophosphamide, BCNU (Carmustine), V, Etoposide (VP-16); Mel, Melphalan, 120 mg/m^2; Mel 200 200 mg/m^2; TBI, Total Body Irradiation.

Statistical methodology

The estimated progression free survival distribution will be obtained using the product-limit based Kaplan Meier method. The Kaplan-Meier methodology will allow for incorporation of censored observations to be possibly expected in this study thereby resulting is a more efficient estimate of the true distribution of progression free survival than if this information was not used. Estimates of quantities such as median survival will be obtained. Using this distributional estimate, summary descriptive statistics, e.g. percentiles, will be obtained. Additionally, a 95% confidence interval of the distribution will be computed based on Greenwood's formula for the variance of the survival function.

Response rates and toxicities will be reported using descriptive statistics. Overall survival for all groups and progression-free survival for amyloid, acute leukemia, and solid tumor patients will be assessed using similar methods as proposed in the primary analyses described above. Exploration of the role of risk factors in outcomes of all treated patients will be done using standard regression

techniques.

Sample size justification

Since no formal hypothesis testing is needed in this study, sample size calculations are based on precision of estimates. Specially, we will consider the projected standard error of the estimated survival probabilities as estimated by Peto's formula. It has the advantage of being a simple estimate which is straightforward to manipulate for sample size calculations and it has been shown to be conservative as compared to Greenwood's estimate of the standard error thereby giving conservative sample sizes. Peto's estimate is of the following form:

$$\sqrt{\frac{\hat{S}(t)\left[1-\hat{S}(t)\right]}{N}}$$

where $\hat{S}(t)$ is the estimated survival distribution and N is the total number of subjects enter into the study. The maximum of the above estimate is achieved at S(t) = 0.5. Using this as a conservative basis for our calculations, it is seen that with the proposed sample sizes the resulting maximum standard error ranges from 0.16 to 0.07.

13.0 GENDER AND MINORITY

Women and members of minority groups and their subpopulations will be included in all study analyses. There is no evidence to that gender or race/ethnicity differences will result in different clinical outcomes.

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15.0 APPENDICES

APPENDIX I

INTERNATIONAL PROGNOSTIC INDEX NHL

Risk Group	Risk Factors, Number	Complete Response (%)	2 Year Survival, %
International index, all patients (n=2031)*			
Low	0 or 1	87	84
Low intermediate	2	67	66
High intermediate	3	55	54
High	4 or 5	44	34
Age-adjusted index, patients ≤60 years (n = 1274)**			
Low	0	92	90
Low intermediate	1	78	79
High intermediate	2	57	59
High	3	46	37

* Risk factors in all patients: Age ≥60 years Serum LDH >1 times normal Performance status ≥2 Stage III or IV disease Extranodal involvement
** Risk factors in patients ≤60 years of age: Stage III or IV disease Serum LDH >1 times normal Performance status ≥2.
Reference: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. NEJM:329, 987-994, 1993

APPENDIX II

TABLE OF AVERAGE WEIGHT FOR HEIGHT AND CALVERT FORMULA FOR CARBOPLATIN DOSING FOR NEUROBLASTOMA PATIENTS

To calculate ideal body weight (IBW) for men:

50 + 0.91x(height in cm – 152)

To calculate ideal body weight (IBW) for women:

45 + 0.91x(height in cm – 152)

To calculate adjusted body weight (ABW) for men and women:

Ideal body weight + [0.25 x (actual body weight – ideal body weight)]

The calculation of ideal body weight is referenced in the package insert of Busulfex® (busulfan) Injection, and also found in the article written by: Gibbs, JP, Gooley, T, Comeau, B, et al, "The Impact of Obesity and Disease on Busulfan Oral Clearance in Adults", *Blood*, Vol 93, No 12 (June 15) 1999: pp 4436-4440.

Calvert Formula for Carboplatin dosing for neuroblastoma patients:

Dose = [(GFR x BSA/1.73) + (15 x BSA)] x 4.1

Dose obtained is ACTUAL dose in mg (NOT mg/kg). GFR is obtained by using a ^{99}Tc-DTPA scan.

BSA is body surface area = square root of the height (cm) x weight (kg)/3600

Calvert Formula for Carboplatin dosing for Adult patients (≥ 18 years of age) with small round blue cell tumors or neuroblastoma

Carboplatin Dose (mg) = (AUC) (Creatinine Clearance (ml/min) +25))
Creatinine Clearance is calculated using the Cockroft-Gault Formula or by 24 hour Urine collection and Creatinine Clearance

Cockroft-Gault Formula: CrCl = ((140-age) (Ideal Body Weight))/((72) (serum creatinine))
(For women, multiply the result by 0.85)

APPENDIX III

GUIDELINES FOR TOTAL BODY IRRADIATION (TBI)

1. **Equipment**:

1. Modality: External photon irradiation
2. Energy: Use radiation of megavoltage quality: i.e., cobalt-60 or accelerator beams with nominal energy of no less than 4 Mev. High energy photons (6 Mev and above) must satisfy the same total dose requirements for skin surfaces. It will be necessary for each institution to establish through experimental measurements whether the combination of entrance plus exit beams satisfy these conditions in the first few millimeters of tissue.
3. Geometry: Single or double head treatment units may be used. Dynamic or static fields may be used. The treatment configuration shall be such that the patient is entirely included within the treatment beam exclusive of the penumbra (i.e., the patient shall be situated well within the 90% decrement line at each depth; the 90% decrement line is defined as a line in each plane perpendicular to the central axis connecting points which are 90% of the central axis dose in that plane). It is essential that agreement between the light and radiation fields be established and verified for the extended TBI treatment distance.
4. Dose Rate: The dose rate shall be between 5 and 25 cGy/min. defined at mid-plane.
5. Treatment Volume: The patient shall be entirely included within the static or sweeping treatment beam. Care should be taken to guarantee that no part of the patient extends into the penumbra region of the beam.

2. **Treatment Dose**:

1. Prescription Point is defined as the point midplane at the level of the umbilicus.
2. Dose Definition: The dose shall be defined as centigray to muscle. No inhomogeneity corrections shall be made in the calculation of the dose to the prescription point.
3. Total Treatment Dose:
    1. For protocol doses of 1200 cGy the total treatment dose shall be delivered in fractions of 200 cGy using a hyperfractionated regimen of 2 fractions per day on 3 consecutive days, with a minimum interval of 6 hrs between fractions.
    2. The protocol total dose of 200 cGy shall be delivered in a single dose fraction for 6 total doses.
4. All patients will be treated in the sitting upright position using the TBI treatment stand. The patient treatment position should be recorded and submitted as part of the quality assurance documentation.
5. Tissue compensators may be used when necessary to improve dose homogeneity. If used, a complete description of compensation technique and its effect on the prescription dose and dose distribution shall be reported and submitted as part of the quality assurance documentation.
6. Skin bolus such as blankets or other body covers may be used to bring up the superficial dose to satisfy the homogeneity requirements. The superficial dose shall be determined at a depth of 2-3 mm.

7. All fields should be treated each fraction.

8. Lung shielding will be utilized for all patients treated with total body irradiation to compensate for the lower density of the lung compared to soft tissues. The total dose to the lung will not exceed 900cGy in the Melphalan/TBI regimen, or 900 cGy in the VCT regimen, but will be as close to it as possible and will never be less than 800cGy. This will be accomplished by using partial lung_cerebend blocks in an alternating fashion between anterior and posterior treatments. The total number of fractions using lung shielding will vary depending on the total prescription dose.

   A margin of approximately 1.5 cm from the chest wall and mediastinal tissues will be used to prevent underdosing of these regions. After a chest x-ray is obtained in the treatment position, the physician will determine the lung volume to be shielded and will draw the shield dimensions. Cerrobend blocks will then be made and verification films will be obtained at each fraction using shielding and checked by a physician to ensure proper coverage. Any adjustments of the lung shields will be made prior to treatment. All patients will be treated in the sitting upright position using the TBI treatment stand. Verification of dose to the lungs will be accomplished by use of diodes at the entrance and exit side of the patient under the partial lung shield to determine the approximate dose to the midline of the patient by averaging the entrance and exit dose.

3. **Calculations and Treatment Planning**: It is recommended that the calculational method be based upon measurements that are made in a unit density phantom 35 x 35 x 35 cm3 in size. All measurements should be made at the appropriate TBI extended SSD. The method of calculation should be specific to the institution's methods and clearly documented.

APPENDIX IV

CRITERIA FOR GRADING TOXICITY

Regimen Related Toxicity in Patients Undergoing BMT

Bearman Sl et al, 1988

	Grade I	Grade II	Grade III
Cardiac	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on CXR with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal	Increase in creatinine up to twice the baseline value (usually the last recorded before start of high dose therapy)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary	Dypsnea without CXR changes not caused by infection or congestive heart failure; or CXR showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	CXR with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO2 (>10% from baseline) but not requiring mechanical ventilation or >50% O2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or >50% oxygen on mask and not caused by infection or CHF

	Grade I	Grade II	Grade III
Hepatic	Mild hepatic dysfunction with bili >2.0 mg% but < 6.0 mg %; or weight gain >2.5 % and < 5 % from baseline of noncardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest prehigh dose therapy	Moderate hepatic dysfunction with bili >6 mg% < 20 mg %; or SGOT increase with > 5-fold from prehigh dose therapy; or clinical ascites or image documented ascites >100ml; or weight gain >5% from baseline of noncardiac origin	Severe hepatic dysfunction with bili > 20 mg %; or hepatic encephalopathy; or ascites compromising respiratory function
CNS	Somnolence but the patient easily arousable and oriented after arousal	Somnolence with confustion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding, or CNS infection	Seizures or coma not explained by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous IV narcotic drug	Pain and/or ulceration requiring a continuous IV narcotic drug	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI	Watery stools >500 ml but <2,000 ml every day not related to infection	Watery stools >2,000 ml every day not related to infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	Ileus requiring nasogastric suction and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

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

APPENDIX V

SOLID TUMOR AND RESPONSE CRITERIA

Table 3 - Definition of best response according to WHO or RECIST criteria*

Therasse et al, 2000

Best Response	WHO change in sum of products	RECIST change in sums longest diameters
CR	Disappearance; confirmed at 4 wks†	Disappearance; confirmed at 4 wks†
PR	50% decrease; confirmed at 4 wks†	30% decrease; confirmed at 4 wks†
SD	Neither PR nor PD criteria met	Neither PR nor PD criteria met
PD	25% increase; no CR, PR, or SD documented before increased disease	20% increase; no CR, PR, or SD documented before increased disease

*WHO = World Health Organization; RECIST = Response Evaluation Criteria in Solid Tumors, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.**

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal

Evaluation of target lesions

	progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

APPENDIX VI

RESPONSE CRITERIA FOR NON-HODGKIN LYMPHOMA AND HL

Cheson et al 1999.

The following criteria are considered anatomic definitions (Table 1). In the future, as additional radiographic, laboratory, and functional studies become more widely available and clearly demonstrate predictive value, they may be recommended as well.

CR requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (eg, lactate dehydrogenase [LDH]) definitely assignable to NHL.

2. All lymph nodes and nodal masses must have regressed to normal size ($\leq$1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to $\leq$ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan are cumbersome and not widely used.35,36 Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate ($\geq$ 20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time. These studies should only be incorporated into trials examining important research questions.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

PR requires the following:

1. ≥ 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features:

   (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by at least 50% in the SPD.

4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, eg, large-cell lymphoma or low-grade lymphoma (ie, small, lymphocytic small cleaved, or mixed small and large cells).

6. No new sites of disease.

Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (CR, CRu) requires the following:

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

2. ≥ 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following:

1. ≥ 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.

2. Appearance of any new lesion during or at the end of therapy.

Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria.

1. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies should be performed no later than 2 months after treatment has been completed to assess response. This interval may vary with the type of treatment, eg, a longer period may be more appropriate for biologic agents where the anticipated time to response may be greater.

2. A bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

Table 1. Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	> 50% decrease	> 50% decrease	Irrelevant
	Decrease in liver/spleen	> 50% decrease	> 50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

APPENDIX VII

The following criteria will be used for ALL as well as AML for determining response.

Response Criteria in Acute Leukemia				
Response Criterion	Time of Assessment	Neutrophils (L)	Platelets (mcL)	Bone Marrow Blasts (%)
Morphologic CRi (absence of leukemia with incomplete count recovery)	Day 100 +/- 20 days post BMT	<1,500	<100,000	< 5
Morphologic CR	Day 100 +/- 20 days post BMT	> 1,500	> 100,000	< 5
Cytogenetic CR	Day 100 +/- 20 days post BMT	> 1,500	> 100,000	< 5
Molecular CR	Day 100 +/- 20 days post BMT	> 1,500	> 100,000	< 5
Partial remission	Day 100 +/- 20 days post BMT	> 1,500	> 100,000	< 50% decrease in blast count or decrease in blast count to 5-25%

Abbreviations: AML, acute myelogenous leukemia; EMD is defined as non-response or progressive disease; CR, complete remission.

APPENDIX VIII

Amyloidosis Response Criteria

Criteria for therapeutic response/outcome assessment (criteria used at Memorial Sloan Kettering Hospital) (Comenzo et al, 1998)

Amyloid-related organ response will be evaluated on the basis of the accepted criteria described below. Based on the criteria below, amyloid-related organ involvement should be scored as improved, stable or worsened at 6 months/1 year after initiation of therapy and annually thereafter.

An improvement of one or more affected organ(s) is defined by:

Kidneys: A 50% reduction in 24-h urine protein excretion in the absence of progressive renal insufficiency.

Heart: A ≥ 2 mm reduction in the mean left ventricular thickness (average of posterior wall and septal thickness) by echocardiogram, or a decrease by two points in NYHA classification (e.g. from 3 to 1).

Liver: A ≥ 50% decrease of an initially elevated alkaline phosphatase level with reduction in the size of the liver by at least 2 cm [determined by ultrasound or computed tomography (CT) scan].

Neuropathy: Clinical improvement supported by clinical history, neurological examination, orthostatic vital signs, resolution of severe constipation or reduction of diarrhea to less than 50% of previous movements per day, and electromyography (EMG) studies if indicated.

Worsening of one or more affected organ(s) is defined by:

Kidneys: Doubling of urinary protein loss if <3 g/24 h at baseline, or 50% increase in urinary protein loss if ≥ 3 g/24 h, or reduction of creatinine clearance by ≥ 50%, or increase in serum creatinine of ≥ 176.9 micromol/l.

Heart: Evidence of echocardiographic progression with an increase in cardiac wall thickness by ≥ 2 mm or a decrease in ejection fraction by ≥ 20%.

Liver: ≥ 50% increase in the alkaline phosphatase level or doubling of serum bilirubin or liver enzymes (aspartate transaminase, alanine transaminase) due to amyloid, or increase in the size of the liver by at least 3 cm (determined by physical examination, ultrasound, or CT).

Neuropathy: Clinical worsening supported by history, worsening orthostatic vital signs and symptoms, and EMG studies if indicated.

Stable disease:

It is defined when none of the criteria for improvement or for worsening disease are met.

Response of the clonal plasma cell disease

Evaluation of the clonal plasma cell disease is based on standard electrophoretic and immunofixation tests of blood and urine for a monoclonal protein (M protein), and bone marrow biopsy stained for isotypic plasma cells. The difference between the serum and/or urine M protein pre- and posttreatment will be calculated. This may be in the form of an M spike or quantifiable immunoglobulin or light chain measurements. The percentage reduction in clonal plasma cell disease will usually be assessed by subtracting the postchemotherapy value from the baseline value, dividing by the baseline value, and multiplying by 100%. A reduction of $\geq$ 50% in this measurement will be considered a 'response'. A > 90% reduction of the M protein with its persistence by immuno-fixation will be considered a 'very good response'. A 'complete response' to therapy requires the M protein to be undetectable by immunofixation of serum and/or urine and normalization of the bone marrow biopsy. Monoclonal immunoglobulins are often difficult to detect or are unquantifiable in many patients with AL amyloidosis using traditional methods. The limitations and inaccuracies of using electrophoresis, etc., are therefore self-evident, and use of fully quantifiable serum FLC measurements are strongly encouraged

APPENDIX IX

Myeloma Response Criteria

(Revised Blade et al 1998)

1. CR = Complete Response and requires ALL of the following:

a. Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation.
The presence of new monoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.

b. <5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein it
is not necessary to repeat the bone marrow unless the patient had non-secretory myeloma.

c. No increase in size or number of lytic bone lesions on radiological investigations, if performed (development of a compression fracture does not exclude response).

d. Disappearance of soft tissue plasmacytomas.

e. For plasma cell leukemia, absence of plasma cells in blood.

(Patients in whom some, but not all, the criteria for CR is fulfilled are classified as PR,
providing the remaining criteria satisfy the requirements for PR. This includes patients in
whom routine electrophoresis is negative but in whom immunofixation has not been performed).

2. CCR = Continuing Complete Response requires ALL of the following:

a. CR continuing from CR prior to high dose therapy.

3. PR = Partial Response requires the following:

a. ≤50% reduction in the level of the serum monoclonal paraprotein, maintained for

a minimum of 6 weeks.
OR
Reduction in 24 hour urinary light chain excretion either by ≥90% or to <200 mg/24 hours in light chain disease.

b. For patients with non-secretory myeloma or plasma cell leukemia only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed.

c. ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

d. No increase in the size or number of lytic bone lesions on radiological investigations. If performed (development of a compression fracture does not exclude response).

e. For plasma cell leukemia, absence of plasma cells in the blood.

(Patients in whom some, but not all, the criteria for PR are fulfilled are classified as MR, providing the remaining criteria satisfy the requirements for MR.)

4. MR = Minimal Response requires all of the following:

a. 25-49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
OR
50-89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 hours, maintained.

b. For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained.

c. 25-49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

d. No increase in the size of number of lytic bone lesions on radiological investigations, if performed (development of a compression fracture does not exclude response).

(MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR).

5. NR = No response

a. Not meeting the criteria of either minimal response or progressive disease.

b. For plasma cell leukemia only, not meeting criteria for CR or PR.

6. SD = Stable Disease

a. Stable values (within 25% above or below value at time response is assessed) maintained for at least 3 months.

7. REL from CR = Relapse from CR requires one or more of the following:

a. Reappearance of serum or urine paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.

b. ≥5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.

c. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions. Development of a compression fracture does not exclude continued response and may not indicate progression.

d. Development of hypercalcaemia (corrected serum Ca >1.5 mg/dl or >2,8 mmol/L) not attributable to any other cause.

e. For plasma cell leukemia, reappearance of plasma cells in blood.

8. PROG = Progressive Disease (for patients not in CR) requires one or more of the following:

a. >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed by at least one repeated investigation.

b. >25% increase in 24 hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hours and confirmed by at least one repeated investigation.

c. >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.

d. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

e. Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).

f. Development of hypercalcemia (corrected serum Ca >1.5 mg/dl or >2.8 mmol/L) not attributable to any other cause.

g. For plasma cell leukemia, reappearance of plasma cells in blood.

APPENDIX XI

Definitions: On/Off Study dates, On/Off Treatment dates

On-Study Date	Start Treatment Date	Stop Treatment Date	Off-Study Date
Date high dose therapy regimen started for first BMT	**Date high dose therapy regimen started for first BMT**	**Date infusion of stem cells is complete (for second BMT unless second BMT is not able to be administered**	**Date of first disease progression post-transplant or date of death due to any cause or at least 60 months of follow-up, whichever comes first"**

****All >/=2nd BMTs and DLIs count toward accrual, except for planned tandem auto BMTs which count once toward accrual.**

APPENDIX XII

Child-Pugh Classification of Liver Failure

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

Child - Pugh Classification:
A = 1 – 6, B = 7 – 9, C = 10-15

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

CLEARANCE (ml/min)
Male = (140-age) x IBW (kg) / 72 x SrCr
Female= male clearance x 0.85

IBW (male) = 50 + 0.91(Height(cm) - 152)
IBW (female) = 45 + 0.91(Height (cm) - 152)
SrCr in mg/dL.

SCHWARTZ FORMULA FOR ESTIMATION OF CREATININE CLEARANCE UP TO AGE 18

CLEARANCE (ml/min/1.73 m2) = K x L / SrCr

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

Age	K
2-12 y	0.55
13-21 y female	0.55
13-21 y male	0.70