Title: A Pilot Study of a Sequential Regimen of Intensive Chemotherapy Followed by Autologous or Allogeneic Transplantation for Refractory Lymphoma (Non-Hodgkin's and Hodgkin's) and an Expansion Phase 2 Cohort

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Weill Cornell Medical College

TITLE: A PILOT STUDY OF A SEQUENTIAL REGIMEN OF INTENSIVE CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS OR ALLOGENEIC TRANSPLANTATION FOR REFRACTORY LYMPHOMA (NON-HODGKIN'S AND HODGKIN'S) AND AN EXPANSION PHASE 2 COHORT

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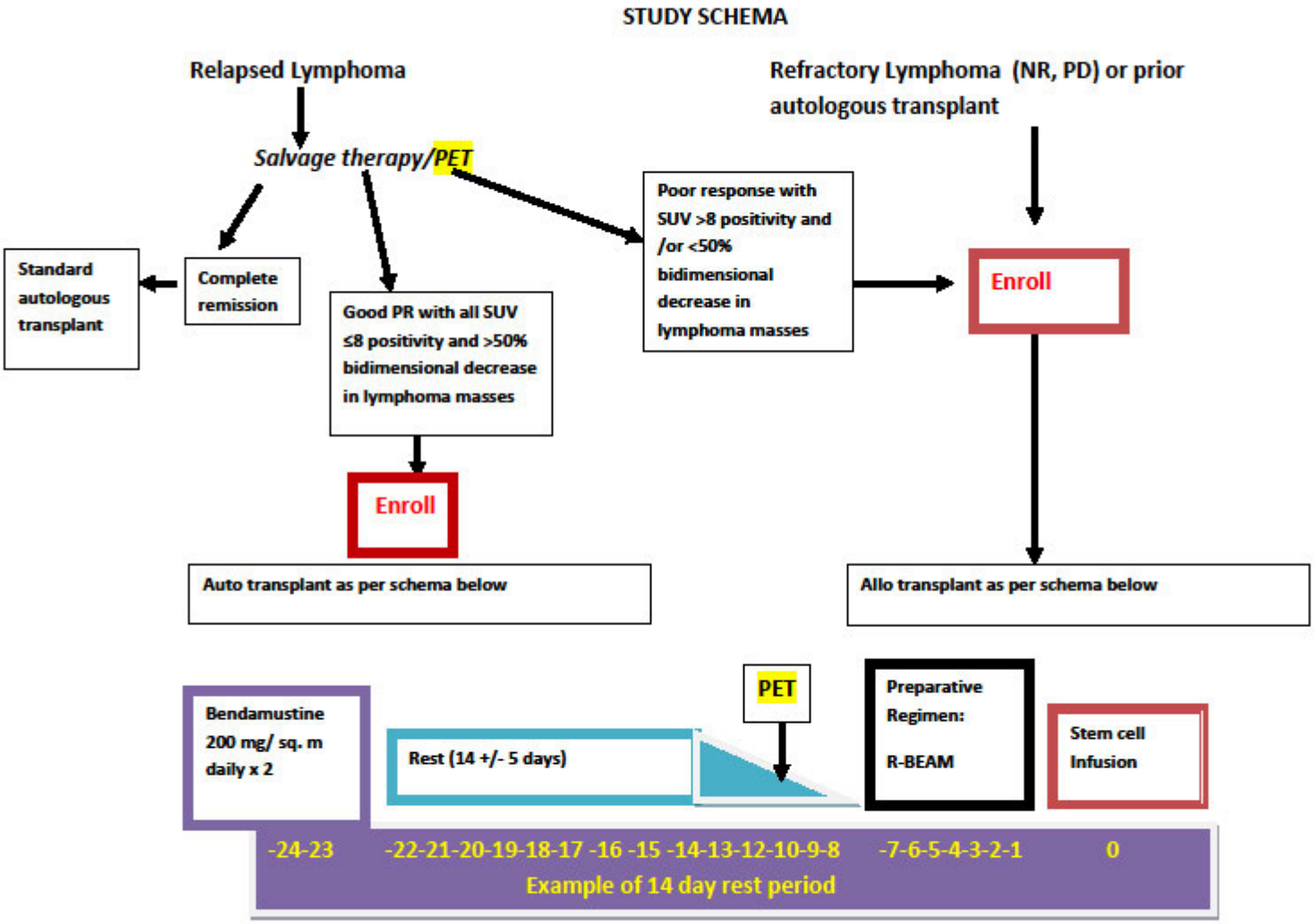
STUDY SCHEMA
Relapsed Lymphoma
Refractory Lymphoma (NR, PD) or prior autologous transplant
Salvage therapy/PET
Standard autologous transplant
Complete remission
Good PR with all SUV ≤8 positivity and >50% bidimensional decrease in lymphoma masses
Poor response with SUV >8 positivity and /or <50% bidimensional decrease in lymphoma masses
Enroll
Enroll
Auto transplant as per schema below
Allo transplant as per schema below
Bendamustine 200 mg/ sq. m daily x 2
Rest (14 +/- 5 days)
PET
Preparative Regimen:
R-BEAM
Stem cell Infusion
-24-23 -22-21-20-19-18-17 -16 -15 -14-13-12-10-9-8 -7-6-5-4-3-2-1 0
Example of 14 day rest period

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1. OBJECTIVES

1.1. Primary Objectives

- To determine the safety and efficacy of high dose bendamustine induction followed by high dose chemotherapy in the treatment of relapsed and refractory lymphoma
- To determine ability to recover after high dose chemotherapy and proceed to transplant within 14 days +/- 5 days from start of bendamustine.

1.2. Secondary Objectives

- Overall Survival (OS) at Days 100 and 360 post transplant
- Disease Free Survival (DFS)
- Response (complete or partial remission, stable disease, progressive disease)
- To determine PET response after treatment with high dose bendamustine
- Transplant Related Mortality (TRM)

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2. BACKGROUND

2.1 Refractory and Relapsed Non-Hodgkin's and Hodgkin's Lymphoma

Refractory is a term that refers to patients that do not respond to treatment, while relapsed patients' malignancies have recurred after treatment. Patients with aggressive Non-Hodgkin's Lymphoma (NHL) and Hodgkin's Lymphoma (HL) that have relapsed after or are refractory to standard induction chemotherapy normally undergo autologous stem cell transplantation if their disease is chemosensitive (i.e. responding) to salvage therapy (therapy used for relapsed disease) . [1]

Traditionally, patients with such chemotherapy sensitive relapses are thought to have cure rates of approximately 50 to 60% with autologous stem cell transplantation (PARMA study). More recent data suggest that patients failing initial treatment with rituximab containing regimens (which constitute the large majority of lymphoma patients) or those with early relapses represent a more unfavorable group.

The CORAL study showed that subjects had only approximately a 20% cure rate with salvage autologous transplant, as did those with early relapses (< 1year)[2]. Subjects' whose disease did not demonstrate chemosensitivity did not benefit from standard autologous transplantation, even with intensified regimens.[1]

Over the past decade PET scanning has emerged as an effective method for assessing chemotherapy responsiveness in patients with refractory or relapsed lymphoma. Also, persistent PET positivity prior to stem cell transplantation is an unfavorable feature and a harbinger of early disease progression. [3], [4],[5], [6]

2.2 **StudyRationale**

Alternative approaches are warranted to improve outcome of patients failing current regimens of front line chemotherapy. A large number of novel drug treatments are under active investigation, but the concept of dose intensification continues to have appeal due to its proven track record in inducing durable remissions, be it in a relatively small percentage of patients.

In our attempt to improve subject outcomes, we will study several modifications to the current standard practice:

1) Dose density combined with dose intensity
2) High dose bendamustine
3) The use of allogeneic transplantation in selected subjects (based on entry criteria).

2.2.1 **Dose Density Combined with Dose Intensity**

Dose density is an approach used to overcome lymphoma resistance to therapy. This method involves giving chemotherapy frequently within a short time frame so as not to allow the malignant clone to recover. One example is the dose dense approach of the German lymphoma group, Pfreundschuh, who used the CHOP regimen every 14 days rather than every 21 days in the front line lymphoma setting. [7] Gianni's group used a high dose sequential chemotherapy approach (dose dense) followed by autologous transplantation for NHL (dose intense). This study showed a marginal benefit over standard chemotherapy and autologous transplant but this could not be reproduced in a multicenter trial due to excessive toxicity.[8]

Dose intensity is the hallmark of high dose chemotherapy regimens, but attempts at both dose intensity and dose density (e.g. double autologous transplant) have often faltered because of inordinate delays between successive cycles of chemotherapy. Examples of this approach include a recent study of tandem autologous transplant for relapsed and refractory lymphoma with the first transplant using myeloablative BEAM as the conditioning regimen and the second transplant using radioimmunotherapy.[9] The estimated 4-year OS and PFS were 67% and 64%, respectively.

A second study of tandem transplants had an overall survival of 59% at 114 months post-transplant, which was better than the standard results noted in the CORAL study for single transplants in this situation.[10] Furthermore, 86% of patients who achieved a complete response (CR) remained alive and disease free for 114 months. Nonetheless, there is a significant time required to recover from one transplant to go on to the next and not all patients are able tomove forward to the 2nd transplant.

Many patients with recurrent NHL and HL have disease that tends to grow quickly, repopulating malignant cells between salvage cycles. Such disease is often characterized by intense uptake on PET scans and, more readily measured, a high serum lactate dehydrogenase (LDH). Such disease may be more effectively addressed

by combinations of dose density and dose intensity. Such approaches have already demonstrated certain success in the front line treatment of lymphoma.
A combination of dose intensity and dose density is used in the French rituximab, doxorubicine, cyclophosphamide, vindesine, bleomycine, prednisolone (R-ACVBP) (ACBVP R) regimen[11]. This study included subjects with diffuse large B-cell lymphoma with 2 or 3 International Prognostic Index factors. Subjects received four cycles of intensive biweekly chemotherapy with R-ACVBP followed by auto-transplantation in responding subjects. This resulted in a in a 78% 4-year overall survival. These results warrant being compared to other approaches.

The approach of giving a high dose salvage regimen followed quickly and sequentially by an allogeneic transplant, timed such that the disease does not have the opportunity to regrow between cycles, has been pioneered in patients with acute leukemia. Patients with refractory leukemia have been treated with an intensive cycle of salvage chemotherapy and then proceeded to allogeneic transplant within 14 days of treatment, with a significant benefit to this approach.[12], [13], [14] This protocol will emulate these protocols in refractory and relapsed lymphoma, using drugs that are standard of care in the treatment of lymphoma, but using the timing/ sequential strategy that has been developed in the refractory leukemia population. Currently, no timing-to-transplant regimen has been approved by the U.S. Food and Drug Administration (FDA). Also, the FDA has not approved any transplant conditioning regimens; only the use of individual drugs.

2.2.2 **High Dose Bendamustine**

Bendamustine is an FDA approved drug that has efficacy in treating lymphoma and has a unique mechanism of action.[15]We propose to use high dose bendamustine at a dose of 200 mg/m2/day for two consecutive daysas a dose intense approach to relapsed and refractory lymphomas prior to proceeding to transplant with BEAM conditioning, a commonly used conditioning regimen. This will be done in a sequential manner so that dose density will also be maximized.

The current standard dose of bendamustine in treating malignancies, such as lymphoma, is 240 mg/m^2 per cycle.[16] In one study. Bendamustine had been used in a conditioning regimen for autologous lymphoma transplants up to 200 mg/m2/day over 2 days, for a total of 400 mg/m2 and this still was not the maximally tolerated dose.[17]In this modified Fibonacci dose-escalation study, subjects received 160-200 mg/m2 daily x2 on days -7 and -6 prior to autologous SCT. Dose escalation proceeded up to the maximum planned dose (400 mg/m2 cumulative) without any non-hematologic dose-limiting toxicity. As prior phase I studies of bendamustine in advanced solid tumors demonstrated cardiac toxicity at 280 mg/m2 as a single dose (not seen when fractionated over 2 days as in the proposed schedule), additional subjects were enrolled and 0 of 6 demonstrated dose-limiting toxicity. Bendamustine has been used in at WCMC as part of a conditioning regimen for auto-transplantation in multiple myeloma. In that study, a dose of 225 mg/m^2 of bendamustine was been combined with melphalan with no major toxicities. [18]

2.2.3 **The Use of Allogeneic Transplantation in Selected Subjects**

Patients with chemotherapy resistant disease or those who have disease progression despite autologous transplantation are often considered for allogeneic transplantation.[19] Allogeneic transplantation offers the benefit of an immunological strategy (graft versus lymphoma effect) in addition to the intensive chemotherapy +/- radiation therapy of the conditioning regimen. For some subjects in this study, allogeneic transplantation will be considered.

The following criteria will be used to determine whether subjects will proceed to autologous or allogeneic transplantation:

<u>Autologous transplantation</u>

- Subjects with relapsed lymphoma who have at least a partial response to their prior salvage regimen defined as:
- PET positivity with SUV ≤ 8and > 50% bidimensional decrease in lymphoma masses.

<u>Allogeneic transplantation</u>

- Subjects with lymphoma who had a prior autologous transplant
  or
- Subjects with refractory lymphoma who did not achieve a partial response to salvage therapy as defined above.

NOTE: The response definitions are outlined in the Cheson criteria (Appendix C)..[20]

2.2.4 **Treatment Justification**

1) The subjects included in this protocol have a low likelihood of durable response to standard salvage therapy and arein great need of new curative options.

2) The protocol is formally designed to assess the toxicity of the entire treatment sequence. But the secondary endpoints include an effort to assess benefits and toxicity of every component (drug and transplant) individually.

3) In some respects this study mirrors current clinical practice and codifiesmanagement that is routinely performed in desperate cases.

3. STUDY DESIGN

Step 1: Bendamustine

Step 2A: BEAM (plus Rituximab if applicable) conditioning and autologous transplant.

OR

Step 2B: BEAM (plus Rituximab if applicable) conditioning and allogeneic transplant.

This pilot study will enroll a total of 30 subjects. With 15 subjects assigned to the autologous transplant cohort (according to disease status and eligibility) and 15 subjects to the allogeneic transplant cohort (according to diseases status and eligibility).

Subjects who do not undergo transplantation will be replaced until both cohorts are filled with 15 allogeneic and 15 autologous subjects. The subjects who do not undergo transplant will be evaluable for toxicity if they underwent the bendamustine chemotherapy.

Once the pilot is completed with reasonable safety and efficacy as reviewed by the DSMB, an expansion phase 2 study will be done to validate the results of the pilot. This will involve enrolling another 60 patients to follow the above algorithm. Patients who do not undergo transplant will be replaced but will be evaluable for bendamustine toxicity.

4. SUBJECT SELECTION

4.1 Inclusion Criteria

- Subjects must have histologically or cytologically confirmed relapsed or primary refractory lymphoma (including Hodgkin's Lymphoma) staged with PET scan to have
    - **Allogeneic arm:**
        - Progressive disease**or**
        - No response to salvage therapy**or**
        - Partial response to salvage therapy defined as≥50% reduction in bidirectional area of masses but SUV remains ≥8 in at least some PET avid areas
        - Prior autologous transplant
    - **Autologous arm:**
        - Partial response of >50% reduction in bidirectional area of masses and SUV reduction to <8 in PET avid areas

Patients with complete response to salvage therapy (i.e. complete resolution of previous lesions and PET consistent with complete response (CR) by Cheson Criteria) are not eligible.

- Subjects must have evaluable disease.
- Subjects must have received at least one induction therapy and one line of salvage therapy that each incorporate at least two drugs that are standard of care for lymphoma
- Age ≥18 years.
- KPS (Karnofsky Performance Score) ≥ 50%
- For autologous transplants: Subjects must have an adequate number of CD34+ stem cells collected to allow for transplantation. This number is defined as ≥ $2x10^6$ CD34+ cells / kg body weight. If not previously collected and stored, the

subject must be willing to undergo stem cell mobilization and collection as per standard practice. If sufficient cells cannot be collected, subjects will be offered the option to proceed with the allogeneic arm of the study.

- Male and female subjects must use an effective contraceptive method during the study and for a minimum of 6 months after study treatment**.** Female subjects of childbearing potential must have a negative serum pregnancy test within 2 weeks prior to enrollment.
- Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

- Known to be positive for HIV
- Subjects may not be receiving any other investigational agents (defined as non FDA-approved agents) at the time of initiating bendamustine regimen. However, the salvage therapy for lymphoma can be part of an ongoing clinical trial with an investigational agent.
- Women who are pregnant or breast feeding. Women of childbearing age must use adequate contraception and have a negative pregnancy test.
- The risks to an unborn fetus or potential risks in nursing infants are unknown.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to any medications listed in the protocol.
- Subject with severely decreased Left Ventricular Ejection Fraction (LVEF) or severely impaired pulmonary function tests (PFT's)
- Uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.3 Donor Selection and Stem Cell Source

Institutional policies regarding criteria and selection of the donor will be followed. Related and unrelated donors will be allowed.

4.4 Hematopoietic Progenitor Cell Source (HPC)

Storage, stem cell source, and handling of HPC will be in accordance with institutional policy.

5. REGISTRATION PROCEDURES

5.1 Central Patient Registration

Subjects will be centrally registered with Weill Cornell Medicine (WCM), Joint Clinical Trials Office (JCTO).To register a subject, fax the following documents to the Clinical Research Office at (646) 962-1610:

- WCMC Subject registration form

- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- Confirmation of sponsor registration, when applicable
- For inpatients, signed consent documentation template

Central registration information is reviewed and entered into the HemOnc centralized research database.

6. ASSESSMENTS

6.1 Pre-Transplant Evaluation

6.1.1 Evaluation at Enrollment-before bendamustine bridge

The following observations are considered standard evaluations for transplant eligibility and should be determined as close to conditioning as possible.

1. Medical history, physical examination, height and weight.[1,2]
2. KPS (Karnofsky Performance Score) ≥ 50%[1,2]
3. Complete blood count (CBC) with differential and platelet count, serum creatinine, BUN, electrolytes, uric acid, Ca, PO_4 , bilirubin, alkaline phosphatase, AL T, AST, LDH, glucose, Mg, protein, albumin, PT, PTT, estimated GFR[1,2]
4. Dental evaluation
5. Sinus imaging, which can include x-rays, CT, PET or MRI scans
6. Cytomegalovirus (CMV) antibody test
7. Infectious disease and hepatitis panel (HepAAb, HepB Sab, HepB Sag, HepB Core Ab, HepCAb), herpes simplex, syphilis, HIV and HTLV 1 antibody, & varicella zoster virus.
8. High resolution HLA typing, if not already performed.º
9. Electrocardiogram (ECG) < 6 weeks before initiation of conditioning therapy.
10. Left ventricular ejection fraction, before initiation of conditioning therapy. It would be necessary to do LVEF testing after completion of any prior cardio toxic drugs.
11. Diffusing capacity the lung for carbon monoxide (DLCO), Forced Expiratory Volume in One Second (FEVI), and Forced Vital Capacity (FVC) or O_2 saturation before initiation of conditioning therapy.[2] It would be necessary to do the pulmonary testing after completion of any prior lung toxic drugs.
12. Bone marrow aspirates and / or biopsies for pathology and cytogenetics[1,2]
13. Beta -HCG serum pregnancy test for females of childbearing potential.
14. Whole body PET/CT scanprior to enrollment.[1,2] It would be necessary to the the PET/ CT after any prior lymphoma therapy has been completed.
15. Chimerism: Peripheral blood for pre-transplant RFLP analysis to establish a reference profile of host hematopoiesis.º,[2]
16. Diagnostic Lumbar Puncture as clinically indicated (High grade lymphoma).

º These evaluations will occur for allogeneic transplants, only

6.1.2. Evaluation after bendamustine but before Transplant conditioning

- Medical history, physical examination, height and weight.[1,2]
- KPS (Karnofsky Performance Score) ≥ 50%[1,2]
- Complete blood count (CBC) with differential and platelet count, serum creatinine, BUN, electrolytes, uric acid, Ca, PO_4 , bilirubin, alkaline phosphatase, AL T, AST, LDH, glucose, Mg, protein, albumin, PT, PTT, estimated GFR[1,2]
- Whole body PET/CT scan

6.2 Post-Transplant Evaluation

The follow-up schedule for scheduled study visits is outlined in Table 1 below.

Table 1

Study Visit	**Target Day Post-Transplant**
1 week	7 ± 4 days
2 week	14 ± 4 days
3 week	21 ± 4 days
4 week	28 ± 4 days
Weeks 5 – 8	At least 2 visits
Day 100 visit	100 +/- 30days
6 month	180 +/- 30 days
12 month	365 ±30 days

The following evaluations are considered standard evaluations for allogeneic transplant recipients. These tests may be adjusted as warranted by clinical circumstances and evolving transplant policy. Please also refer to institutional transplant work up guidelines.

1. History and physical exam to assess GVHD and other morbidity at each visit. CBC at least three times a week from Day 0 until ANC > 500 mm3 for 3 days after nadir reached. Thereafter, CBC at each visit.
2. Creatinine, bilirubin, alkaline phosphatase, AL T, AST, LDH, sodium, magnesium, potassium, and chloride tests twice a week until Day 28 (or four weeks) and then at each visit.
3. Peripheral blood on Days 28, 56, 100, 180, and 365 (or as close to those time frames as possible) for post-transplant chimerism assay
4. Immunizations will be given per institutional guidelines and will follow CDC guidelines.
5. Toxicity assessments post-transplant on Days 28, 100, 180, and 360 or as close to those days as possible.
6. Disease status (PET) evaluation required post-transplant on Days 28, 100, 180 and 1 year post-transplant (or as close to those days as possible).

Testing to determine disease status with PET scans should follow pre-transplant evaluation process. The follow-up schedule for scheduled study visits is outlined in Table 2.

Table 2

Study Assess-ments	**Days after Transplantation**									
	Baseline	After Benda before SCT	7	14	21	28	Weeks 5-8 (SOC)[7]	100	180	365
History, physical exam, weight, height, and KPS	X	X	X	X	X	X	X	X	X	X
CBC[1] , differential, platelet count, and blood chemistries[2]	X									
Infectious disease	X									
Dental exam	X									
Lumbar puncture[5]	X									
Sinus Imaging	X									
ECG, LVEF, or shortening fraction	X									
DLCO, FEV I and FVC or 02-saturation	X							X		
Bone marrow biopsy and aspirate for pathology[4]	X	X			X	X		X	X	X
PET/CT	X	X				X		X	X	X
B-HCG	X									
GVHD and Toxicity assessments	X		X	X	X	X	X	X	X	X
Chimerism	X					X	X	X	X	X

Notes (Table 2):

1. CBC performed at least three times a week from Day 0 until ANC >500 mcL for three days after nadir. CBC performed twice weekly until Day 28. CBC performed weekly after Day 28 until 12 weeks post-transplant.
2. Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST, and ALT, LDH, sodium, magnesium, potassium, and chloride (where standard of care should be according to institutional guidelines). Blood chemistries performed twice weekly until Day 28. Blood chemistries performed weekly after Day 28 until 12 weeks post-transplant.
3. Infectious disease titers include: CMV, Hepatitis panel (HepA, Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV III antibody, and varicella zoster.
4. Bone marrow biopsy and aspirates to pathology required at Day 21 if WBC < 500. Day 28 only to be done if slow neutrophil recovery to evaluate for graft failure. Cytogenics and flow cytometry should be sent as clinically indicated by subject's diagnosis. Pre-SCT bone marrow should only be repeated if previous bone marrow involvement was present. This should be done prior to the bendamustine. If positive, it should be done again prior to the transplant conditioning.
   Post SCT (d 28, d100 etc.) should only be repeated if previously positive, and after allogeneic transplant.
5. If clinically indicated for high grade lymphoma.
6. GVHD assessments only in allogeneic transplant recipients.
7. SOC is standard of care

7. TREATMENT PLAN

7.1 Agents Administration

Treatment will be administered on an *inpatient and/or outpatient* basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for *Investigational Agents* are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

All drugs used in this protocol will be commercially available.

Subjects maybe admitted to the hospital for a period of four to six weeks, sometimes more if necessary for subject care prior to transplant.

7.1.1 Bendamustine Bridge

Subjects on this protocol will receive bendamustine at a dose of 200 mg/ m^2/ day over 60 minutes, on Days – 24 and Day – 23 followed by a short break of 14 +/- 5 days. The number of days the break for each subject will be dependent on multiple factors including donor dates, availability of donor, and weekend infusions versus weekday infusions.

7.1.2 Conditioning Regimen and Transplantation

7.1.2.1 Regimen for *Related* Marrow or Peripheral Blood Stem Cell Transplantation

Drug	Day -6	Day -5	Day -4	Day -3	Day -2	Day-1	Day 0
Carmustine[1]	300mg/ m2						Stem cell infusion
Etoposide[2]		100mg/m2	100mg/m2	100mg/m2	100mg/m2		
Cytarabine[3]		200mg/m2	200mg/m2	200mg/m2	200mg/m2		
Melphalan						140mg/m2	
Campath			20 mg/m2	20 mg/m2	20 mg/m2		

*Pre-medications to prevent Campath toxicities are acetaminophen, Diphenhydramine, Methylprednisolone or Hydrocortisone will be given if necessary.
1) Carmustine – administered over 6 hours
2) Etoposide – administered every 12 hours Day -5 – Day -2
3) Cytarabine – administered every 12 hours Day -5 – Day -2

7.1.2.2 **Regimen for *Unrelated* Marrow or Peripheral Blood Stem Cell Transplantation**

	Day -6	Day -5	Day -4	Day -3	Day -2	Day-1	Day 0
Carmustine[1]	300mg/m2						Stem cell infusion
Etoposide[2]		100mg/m2	100mg/m2	100mg/m2	100mg/m2		
Cytarabine[3]		200mg/m2	200mg/m2	200mg/m2	200mg/m2		
Melphalan						140mg/m2	
Campath	20 mg/m2	20mg/ m2	20 mg/m2	20 mg/m2	20 mg /m2		

*Pre-medications to prevent Campath toxicities are acetaminophen, Diphenhydramine, Methylprednisolone or Hydrocortisone will be given if necessary.

1) Carmustine – administered over 6 hours
2) Etoposide – administered every 12 hours Day -5 – Day -2
3)Cytarabine – administered every 12 hours Day -5 – Day -2

For patients who cannot receive BEAM conditioning therapy, alternative conditioning regimens may be utilized (including but not limited to: Flu Mel, Flu Mel TBI, Cy/ TBI, VP16/TBI). Such

decisions will be addressed within the BMT physician team. This is often the case in patients who had prior BEAM with an autologous transplant and now require a different regimen for an allogeneic transplant.

For patients who do not have an HLA compatible related or unrelated donor, alternative donors may be used such as haplo/ cord or double cord transplants. In such cases, ATG will be substituted for Campath and Flu Mel +/- TBI will be substituted as the conditioning regimen. These regimens are standard of care regimens within the BMT program.

	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1 or day 0
Fludarabine	30 mg/ m^2	30 mg/m^2	30 mg/m^2	30 mg/m^2	30mg/ m^2			Haplo Stem Cell	UCB stem cell
Melphalan						140 mg/m^2			
rATG			1.5 mg/kg		1.5 mg/kg		1.5 mg/kg		
TBI*				2 Grey	2 Grey				

Fludarabine: Administer 30 mg/m2 /day intravenously x 5 days (Day -7 to Day -3) of a total dose of 150 mg/m2. Fludarabine will be dosed according to actual body weight.

Melphalan: Administer 140mg/m2/day intravenously on day -2. Melphalan will be dosed according to actual body weight. Cryotherapy with ice chips will be administered to prevent mucositis.

Rabbit ATG (rATG)-thymoglobulin: 1.5 mg/kg/day IV x3 days total for all patients. ATG will be dosed according to actual body weight. The first dose will be infused over at least six hours, and subsequent doses over at least 4 hours. Pre-medications include acetaminophen 650 mg by mouth, diphenhydramine 25-50 mg by mouth or intravenously, and methylprednisolone 2 mg/kg (1 mg/ kg at the initiation and 1 mg/kg half-way through anti-thymocyte globulin administration). Circumstances may require minor changes in scheduling of chemotherapy. Variations of up to 24 hours in scheduling will be acceptable.

TBI*: Because of occasional cases of graft failure, conditioning has been intensified for certain groups of patients. Patients at high risk for CNS relapse (e.g ALL or Burkitt's) or patients at high risk for graft rejection (i.e., donor-specific HLA antibodies, patients with severe aplastic anemia, or hemoglobinopathies) may receive 2 doses of TBI as part of the conditioning. In rare cases , full dose TBI (1200 Grey) will be part of the regimen if the other regimens cannot be used.

7.1.2.3 Regimen for Autologous Transplantation

	Day -6	Day -5	Day -4	Day -3	Day -2	Day-1	Day 0
Carmustine	300 mg/m2 over 6 hours						Stem cell infusion
Etoposide		100 mg/m2 q12h	100 mg/m2 q12h	100 mg/m2 q12h	100 mg/m2 q12h		
Cytarabine		200 mg/m2 q12h	200 mg/m2 q12h	200 mg/m2 q12h	200 mg/m2 q12h		
Melphalan						140 mg/m2	

Autologous hematopoietic stem cells will be infused on day 0 using standard infusion technique.

7.1.3 **Rituximab**

Subjects with pathological confirmed B-cell malignancies will receive rituximab 375 mg/m^2 on Days + 1 and +8 post -transplant. Subjects with T-cell lymphoma will be enrolled in the study but will not receive rituximab.

Rituximab is FDA approved for B cell malignancies at this dose and schedule. However, as stated earlier, the FDA does not approve transplant regimens. Using rituximab has been utilized in many transplant published studies.

7.1.4 **GVHD Prophylaxis for Related and Unrelated Transplants**

Subjects will receive the drug tacrolimus (Prograf ®) starting before transplant to reduce the risks of graft versus host disease and to promote the growth of the graft.

Tacrolimus will be given at a dose of 0.03 mg/kg/day using continuous intravenous infusion over 24 hours from Day -2 until engraftment or when subject is able to take orally, then a tacrolimus dosage of (approximately) 0.09 mg/kg orally in 2 divided doses. Tacrolimus should be given at full dose to maintain levels of 5-15 ng/mL through Day 100 for related transplants and through Day 180 for unrelated transplants, tapered by 20% every week thereafter. In the presence of GVHD, a clinical decision by the Attending Physician will determine if tacrolimus can be tapered or should be continued. PO tacrolimus can be used in the pre-engraftment period when IV-access for tacrolimus is not available.

7.1.**5 GVHD Prophylaxis for Alternative Donor Haplo/Cord and Double Cord Transplants**

Patients undergoing haplo cord transplant in this protocol will receive the following GVHD prophylaxis in addition to ATG;

Subjects will receive the drug tacrolimus (Prograf ®) and another immunosuppressant, mycophenolate mofetil (Cellcept ®), starting before transplant also to reduce the risks of graft versus host disease and to promote the growth of the graft.

Tacrolimus: 0.03 mg/kg/day using continuous intravenous infusion over 24 hour time period from Day -2 until engraftment or when subject is able to take by mouth, then tacrolimus approximately 0.09 mg/kg by mouth in 2 divided doses. Tacrolimus should be given at full dose to maintain levels of 5-15 ng/mL through approximately Day 180, tapered by 20% every week thereafter. Infection ,toxicity or other clinical circumstances may prompt earlier discontinuation. In the presence of GVHD, a clinical decision by the attending physician will determine if tacrolimus can be tapered or should be continued. PO tacrolimus can be used in the pre-engraftment period when IV access for tacrolimus is not available.

Mycophenolate mofetil (MMF): will be started on Day -2 and given at a dose of 1000 mg every 8 hours until Day 28. Earlier discontinuation, dose adjustments or more prolonged administration may be required for clinical reasons. MMF may be given PO or IV. . Infection, toxicity, very low patient weight (<50kg) may prompt earlier discontinuation or adjustment of doses

7.2 **Mobilization and Stem Cell Collection of Donors**

Pre-screened donors will receive filgrastim according to institutional guidelines prior to collection. Hematopoeitic stem cell collection will be done via temporary large bore catheters or via peripheral access for approximately 1 - 2 days for approximately 3 - 4 hours per day. Goals for the collection are at least 2.5 x 10^{6} CD 34 cells per kg of recipient's weight. There will be no T cell depletion.

On rare occasions, stem cells will be obtained using standard bone marrow harvesting techniques. Peripheral blood stem cell collection will be the preferred method of collection but ultimately it is the donor's choice as to what type of stem cells collection is done

7.3 **General Concomitant Medication and Supportive Care Guidelines**

Subjects will receive supportive care according to institutional guidelines.

All subjects will be offered Neulasta after the bendamustine to avoid neutropenia between the bendamustine and the conditioning regimen. The dose will be the standard FDA-approved dose of Neulasta.

All subjects, regardless of disease histology will receive filgrastim (G-CSF) to speed up the recovery of stem cells. 5 mcg/kg (rounded to 300 mcg or 480 mcg, depending on subject weight) of filgrastim will be administered subcutaneously daily, as per institutional standard of care practice until Absolute Neutrophil Count (ANC) >5 x10E9/L.

Infectious Disease prophylaxis and management will be administered as per the institution's standard of care. Chimerism will be evaluated in allogeneic transplants at Baseline, Days +28, +56, + 100, +180, and +365 or more frequently if there is concern re-graft loss/relapse.

7.4 **Duration of Therapy and Criteria for Removal from Study**

Withdrawal from the trial must be fully documented. The documentation must include reasons for withdrawal and details of any adverse events followed until symptoms resolved. A Final Summary Statement must be completed.

Criteria for discontinuing protocol therapy:

- If the investigator feels that a change of therapy would be in the best interest of the subject
- If the subject requests discontinuation provided that the subject has been counseled again regarding the danger of discontinuation prior to infusion of stem cells after the conditioning regimen.
- If the study drug(s) exhibits unacceptable toxicity
- Intercurrent illness that would interfere with the assessment of clinical status to a significant degree or would prevent further administration of treatment
- Disease progression
- Pregnancy or a positive pregnancy test

7.5 **Duration of Follow Up**

Subjects will be followed up to 3 years after removal from study or until death, whichever occurs first. Subjects removed from the study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event(s).

8. DOSING DELAYS/DOSE MODIFICATIONS

None applicable

9. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

The principal investigator is responsible for monitoring the safety of subjects who enroll in the study. All AEs occurring after any administration of the study drug(s) will be followed until resolution

9.1 Study Agents Risks

All risks for drugs given to subjects within this protocol will be outlined in the Investigator's Brochure. Additional information is in Appendix C – Background Drug Information. Risks for each drug will be specifically listed for subjects in the informed consent form.

9.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

9.3 Recording of Adverse Events

All Grade 3-4 adverse events which are possibly related to the study and unexpected will be recorded on a IRB's adverse event log. The AE log will be maintained by the research staff and kept in the subject's research chart. Hematologic AE's will not be tracked since they are an expected consequence of transplant. Some other grade 3-4 AE that are expected in stem cell transplant will not be collected (e.g. alopecia).

9.4 Serious Adverse Event (SAE) Reporting

9.4.1 Definition of SAE

SERIOUS ADVERSE EVENTS include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition

A serious adverse event (SAE) is any adverse drug experience that occurs at any dose that results in any of the following outcomes:

- Death.
- Life-threatening adverse drug experience.*
- Requires inpatient hospitalization or prolongation of existing hospitalization for deemed unexpected events. For the purpose of this study, hospitalizations for protocol-scheduled procedures, blood product transfusions, social reasons (ie, awaiting transport home), or deemed expected events will not be considered SAEs.
- Persistent or significant disability/incapacity.**
- A congenital anomaly/birth defect.
- Is an important medical event***
- Suspected positive pregnancy

*"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

**"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

***Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious.

Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.4.2 **Reporting of SAE to IRB**

All SAEs occurring on this study will be reported to the IRB according to the IRB policy. The IRB requires immediate reporting of all unexpected and study-related (definite or probable) adverse events. The following procedure will be followed for reporting SAE to the IRB:

- Complete the SAE Cover Sheet (See Appendix B)
- If the event is unexpected AND definitely or probably related to the study, complete the IRB Unexpected, Study-related Adverse Events, Incidents, and Information Reporting Form. This form should be submitted within 24 business hours of investigator notification of the event.

- If the event is expected OR possibly or unrelated to the study, only the SAE Cover Sheet must be completed. These events will be reported to the IRB at the time of continuing renewal on the Adverse Event & IND Safety Reporting Cumulative Table.

Forms may also be downloaded from the IRB website at:
http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html

9.4.3 Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA.

CBER INDs:
Center for Biologics Evaluation and Research
Food and Drug Administration
Suite 200N 1401 Rockville Pike
Rockville, MD 20852-1448

The phone number of the CBER is: 800-835-4709

10. DATA REPORTING AND COLLECTION

10.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, and efficacy data for all enrolled subjects. This is a trial to assess the feasibility including both safety and possible efficacy of a total sequential approach to treating refractory and relapsed Non-Hodgkin's and Hodgkin's lymphoma subjects.

10.2 Accuracy of Data Collection

The Principal Investigator will be the final arbiter of toxicity should a difference of opinion exist.

10.3 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

10.4 Protocol Compliance

Subjects will be reviewed weekly during admission by the study investigators who will score the subject for standard endpoints. After discharge they will be reviewed at least once a month according to the protocol schedule.

11. STATISTICAL CONSIDERATIONS

11.1 Study Endpoints

Primary Endpoints:

- Proportion of patients able to proceed to transplant within 14 days of starting bendamustine and recover after transplant as determined by:

  1) *Engraftment:* This will be defined as a neutrophil count of 500 /mm3 and a platelet count of 20,000 without platelet support for at least one week.

  2) *Regimen related toxicity:* This will be assessed using CTCAE version 4

- Hematologic toxicity will not be taken into account.

Secondary Endpoints:

- *Disease Response:* This will be defined as complete response, partial response, no response, progression according to Cheson Criteria (Appendix C). *Response will be assessed after the bendamustine and again after the transplant.*

- *Progression – Free Survival*: This will be defined as survival free of progression of disease starting from the day bendamustine starts and also calculated from day 0 of the transplant.

- *Survival:* This will be defined in days post initiation of bendamustine and also recalculated as the numbers of days post-transplant and will be specifically evaluated at Day 100, one year and overall survival.

- *Transplant Related Mortality (TRM):* Death due to treatment within the first 100 days.

Note: Acute GVHD will be scored according to the criteria proposed by Przepiorka et al. (Appendix E). Chronic GVHD will be scored according to the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease (Appendix F).

Subject will have toxicity assessments using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 criteria and response assessments as per PET/CT after each stage of this multifaceted approach.

11.2 Sample Size, Analysis Plan and Accrual Rate

Because this is a pilot study, no formal sample size calculation is required and the primary endpoint will be assessed descriptively. However, with 15 subjects completing protocol-based requirements on both the allogeneic arm and autologous arm of the

study, 95% confidence intervals for the proportion of subjects who are able to proceed to transplant and recover after transplant can be constructed to be within ± 20.2% of the true proportion of such patients in the allogeneic arm and within ± 11.0% of the true proportion of such patients in the autologous arm. These calculations assume that the proportion of such subjects who are able to proceed to transplant and recover after transplant is 80% and 95% in the allogeneic and autologous arms, respectively.

The proportion of subjects able to proceed to transplant within 14 days after starting bendamustine and recover after transplant (i.e., primary endpoint) will be calculated and a 95% confidence interval (95% CI) will be estimated via binomial proportions. Secondary endpoints of disease response and transplant-related mortality (i.e., proportions and 95% CI) will also be estimated via binomial proportions. Secondary endpoints of progression-free and overall survival will be assessed by Kaplan-Meier survival analysis.Greenwood's formula will be used to calculate 95% confidence intervals for the Kaplan-Meier survival estimates.

The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level (for exploratory analyses comparing secondary endpoints between arms). All analyses will be performed in SAS Version 9.3 (SAS Institute, Inc., Cary, NC) and STATA Version 12.0 (StataCorp, College Station, TX).

It is expected that the study will accrue 15 subjects per year and accrual will last approximately 24 months. The expansion phase of the additional 60 patients will accrue over 3 years.

11.3 **Toxicity Stopping Guidelines**

The following toxicity stopping guidelines serve as a trigger for additional review by the protocol team and Data Safety Monitoring Board (DSMB), and are not formal "stopping rules" that would mandate automatic closure of study enrollment.

11.3.1**Transplant-Related Mortality (TRM)**

Non-relapse deaths in the first 100 days will be monitored. A TRM rate of > 20% of subjects in the first 6 months within the allogeneic cohort and > 5% of subjects in the autologous cohort would be unexpected. This would be reported to the DSMB and, subsequently, the research team will immediately review the data and protocol should this rate be exceeded. Entry of subjects into the trial will be stopped while the protocol and deaths are reviewed.

11.3.2 **Graft Failure**

Failure to engraft by Day 35 is expected to occur in <=10% of subjects with this approach. A graft failure/graft rejection rate of > 10% would be unexpected and the

research team and DSMB will review the data and protocol should this rate be exceeded. Failure to engraft will be defined as lack of evidence of hematopoietic recovery (ANC < 500/mm3 and platelet count < 20,000/mm3) by Day +35, confirmed by a biopsy revealing a marrow cellularity < 5%. Secondary graft failure will be defined as initial myeloid engraftment by day +35, documented to be of donor origin, followed by a drop in the ANC to < 500/mm3 for more than three days, independent of any myelosuppressive drugs, severe GVHD, CMV, or other infection.

Graft rejection will be defined as graft failure with documentation of return of recipient hematopoiesis as determined by cytogenetic and/or chimerism studies. If there is evidence that the Day 35 graft failure rate is more than 10%, entry of subjects into the trial will be stopped while the protocol and failures are reviewed.

11. 4 **Reporting**

11.4.1 **Evaluation of toxicity:** All subjects will be evaluable for toxicity from the time of their first treatment.

11.4.2 **Evaluation of response:**All subjects included in the study will be assessed for response to treatment.

12. DATA SAFETY MONITORING BOARD

The Data Safety Monitoring Board (DSMB) is being requested to review safety data and to make recommendations regarding continuation, termination, or modification to the study. The research team will report all adverse events to the DSMB per their reporting policies. The DSMB will be constituted at Weill Cornell Medical College and will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population.

The purpose of the DSMB is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DSMB may request additional meetings or safety reports as deemed necessary upon discussion with the research team. The Principal Investigator, Dr. Tsiporah Shore will be the safety contact for all DSMB related analysis outcomes.

Dr. Shore's office is located at:
NYPH-WCMC
520 E 70th St., F364
New York, NY 10021
Phone 212-746-2646

The research team will report all adverse events to the DSMB per their reporting policies. They will convene every six months to discuss outcomes of the ongoing trial. They will be informed of the results of the interim analysis and they will have the authority to close the study in the interest of subject safety if they feel that one of the arms is clearly inferior or for futility.

12.1 **Interim Analysis**

The first 3 subjects in the autologous arm and the first 3 subjects in the allogeneic arm will be reviewed in order to determine if it is safe to continue enrolling on each arm. The DSMB may stop the study following review of results from each interim analysis. Once the first 3 are reviewed, the DSMB will meet to monitor the study every six months to discuss outcomes of the ongoing trial. Appropriate efficacy and safety data summaries will be provided to the DSMB after each interim analysis.

The binomial distribution will be used to establish pre-specified stopping/review guidelines for toxicity. A binomal distribution probability greater than 10% (i.e., estimated based on xsubjects with toxicity among 3 enrolled subjects in each cohort) will be chosen as the threshold for initiating a DSMB stopping and review of the cohort(s). As detailed above, a TRM rate of >20% in the allogeneic cohort would be unexpected. Assuming a TRM rate of 20% in the allogeneic cohort and utilizing the binomial distribution, the probability that 1 out of 3 enrolled subjects will experience TRM is 0.38 (and thus >10%). Therefore, if 1 or more of the first 3 enrolled subjects experience TRM in the allogeneic cohort, the study cohort will be halted and reviewed by the DSMB. Similarly, a TRM rate of >5% in the autologous cohort would be unexpected. Assuming a TRM rate of 5% in the autologous cohort and utilizing the binomial distribution, the probability that 1 out of 3 enrolled subjects will experience TRM is 0.14 (and thus >10%). Therefore, if 1 or more of the first 3 enrolled subjects experience TRM in the autologous cohort, the study cohort will be halted and reviewed by the DSMB. This process will repeat for each set of three enrolled subjects in the cohorts.

As detailed above, a graft failure/graft rejection rate of >10% in the study would be unexpected. Assuming a graft failure/graft rejection rate of 10% in the study and utilizing the binomial distribution, the probability that 1 out of 3 enrolled subjects will experience graft failure/graft rejection is 0.24 (and thus >10%). Therefore, if 1 or more of the first 3 enrolled subjects experience graft failure/graft rejection in the study, the study will be halted and reviewed by the DSMB. This process will repeat for each set of three enrolled subjects in the cohorts.

13. REGULATORY CONSIDERATIONS

13.1 **Institutional Review Board/Ethics Committee Approval**

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

The investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

13.2 **Informed Consent Procedures**

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedure as per GCP's as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. At the pre-admission consultation, patients will be fully informed as to the purposes and potential risks and benefits involved in this study. Subjects will have ample opportunity to ask questions before consenting. Legal guardians will sign informed consent for legally incompetent patients in accordance with hospital policy.

13.3 **Protocol Amendments and Deviations**

Any amendment to this protocol must be agreed to by the Principal Investigator. Written verification of IRB/EC approval will be obtained before any amendment, which affects subject safety or efficacy, is implemented. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

All protocol amendments and consent form modifications will be made by the Principal Investigator.

13.4 **Protecting Privacy and Confidentiality**

Confidentiality will be maintained within the limits of the law. Patient names or any other identifying information will not be used in reports or publications resulting from this study. Only qualified staff from New York Presbyterian Hospital, Weill Medical College of Cornell University, the Food and Drug Administration, will be able to review subject medical records.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5 **Study records requirements**

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of case report forms (CRF) and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

13.6 **Protection of Human Rights**

Participation in this trial is voluntary. All subjects will be required to sign a statement of informed consent, which must conform to Weill Cornell Medical College IRB guidelines.

13.7 **Premature Discontinuation of Study**

The responsible local clinical Investigator has the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.
- Serious adverse events, intolerability of drug regimen, or sudden/unexpected death in any of the early trial (up to three patients) participants

The investigator reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g. IRB/EC, regulatory authorities, etc.).

13.8 **Benefits of the Protocol**

The potential benefit of this study is the development of a safe and effective treatment program for lymphoma patients who have relapsed/ refractory disease. Knowledge will be acquired about this treatment program, its tolerability, and the effectiveness of high dose bendamustine in combination with BEAM conditioning prior to stem cell transplant and the benefit of maintenance lenalidomide in the treatment of relapsed or refractory lymphoma. If effective, this treatment plan may improve disease-free and overall survival in such lymphoma patients.

13.9 **Risks in Relation to Anticipated Benefit**

The risks associated with participation in this trial are commensurate with the expected risks of other potential therapies and are reasonable given the potential benefit to patients with newly aggressive lymphoma. If this sequential approach is as effective against relapsed/ refractory lymphoma as anticipated, this regimen could become standard of care leading to improved survival.

13.10 **Alternative Treatments**

Subjects who refuse to participate in the study or decided to withdrawal from the study will be given the option to choose standard chemotherapy, other investigation studies, supportive care, or no anti-cancer treatment at all. Therapy with an autologous stem cell transplant using standard BEAM conditioning alone may be of benefit. While the results of these therapies have resulted in a low percentage of durable long term remissions, few subjects are cured and none of the drugs used in these standard treatments are free of side effects. We believe that this novel regimen will improve response rates and duration of remission.

13.11 **Incentives**

No incentives will be offered to subjects for participation in the study. Participation is voluntary.

13.12 **Costs**

Subjects and/or their medical insurance coverage will be responsible for paying for their hospitalization, doctor visits, diagnostic tests, chemotherapy (commercially available) drugs, and other medicines used in their care directly. These costs are expected to be equivalent to those that are standard of care.

APPENDIX A

Performance Status Criterias (ECOG and Karnofsky)

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

WCMC IRB SAE Reporting Forms

http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html

APPENDIX C: CHESON CRITERIA

Table 2
Response definitions for clinical trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Complete remission (CR)	Disappearance of all evidence of disease	a. Fluorodeoxyglucose (FDG)-avid or positron emission tomography (PET) + before therapy: mass of any size permitted if PET- b. Variably FDG-avid or PET-: regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy, if indeterminate by morphology immunohistochemistry should be negative
Partial remission (PR)	Regression of measurable disease and no new sites	≥50% decrease in sum of the product of the diameters (SPD) of up to six largest dominant masses. No increase in size of other nodes a. FDG-avid or PET + before therapy: one or more PET + at previously involved site b. Variably FDG-avid or PET-: regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter), no increase in size of liver or spleen	Irrelevant if positive before therapy; cell type should be specified.
Stable disease (SD)	Failure to attain CR/PR or PD	a. FDG-avid or PET + before therapy: PET + at prior sites of disease and no new sites on CT or PET b. Variably FDG-avid or PET-: no change in size of previous lesions on CT		
Relapsed or progressive disease	Any new lesion or increase from nadir by ≥50% of previously involved sites	Appearance of a new lesion >1.5 in any axis ≥50% increase in the longest diameter of a previously identified node >1 cm in short axis or in the SPD of more than one node Lesions PET + if FDG-avid lymphoma or PET + before therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

From Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86. Reprinted with permission of the American Society of Clinical Oncology.

APPENDIX D: PACKAGE INSERT FOR BENDAMUSTINE

APPENDIX E: BACKGROUND DRUG INFORMATION

DRUG FORMULATION, AVAILABILITY, AND PREPARATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment will undertake the preparation, handling and safe disposal of chemotherapeutic agents in a self-contained, protective environment. Unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents will be disposed (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

FILGRASTIM (G-CSF: Granulocyte Colony Stimulating Factor, Neupogen®)

AVAILABILITY
G-CSF is commercially available in 1.0 and 1.6 mL vials containing 300 mcg and 480 mcg G-CSF, and in prefilled syringes containing 300 mcg/0.5 mL and 480 mcg/0.8 mL.

STORAGE & STABILITY
Intact vials and prefilled syringes should be stored under refrigeration. Do not allow the drug to freeze.

ADMINISTRATION
The daily dose of G-CSF should be injected subcutaneously in one or two sites. The dose following peripheral blood stem cell infusion is 5 mcg/kg/day. The dose of G-CSF may be rounded up to the nearest vial size.

TOXICITY
The most common side effect associated with G-CSF is bone pain. Bone pain is usually reported as mild or moderate and, if necessary, may be treated with non-opiod or opiod analgesics.

MELPHALAN(Alkeran®)

AVAILABILITY
Melphalan for IV use is commercially available in sterile 50 mg vials. The product is a lyophilized powder with 20 mg povidone per vial. Also provided is 10 mL of special diluent for use in reconstituting the product. The special diluent has 0.20 g sodium citrate, 6 mL propylene glycol, 0.5 mL 95% ethanol, and sterile water.

STORAGE & STABILITY
Intact vials should be stored at room temperature (15^{o}C-30^{o}C) and protected from light. Reconstituted solutions are chemically and physically stable for at least 90 minutes at room temperature. Solutions further diluted in 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL are stable for at least 60 minutes. Solutions diluted to 1 mg/mL are reported to be physically stable for at least 4 hours at room temperature-chemical stability of this dilution is not known. Because of the relative instability of melphalan solutions, it is recommended that administration of the diluted solution be completed within 60 minutes of reconstitution. Reconstituted solutions should not be refrigerated.

PREPARATION
Melphalan should be prepared immediately before intended use. Each vial is reconstituted with 10 mL of the special diluent to yield a concentration of 5 mg/mL. The reconstituted solution may be diluted with 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL.

ADMINISTRATION

The total dose of melphalan will be administered by short IV infusion over 30-60 minutes, as per institutional pharmacy guidelines.

TOXICITY
The major toxicity of melphalan is bone marrow suppression, usually lasting four to eight weeks. Other toxicities include nausea, vomiting, diarrhea, and mucositis. Less common toxicities include pulmonary fibrosis, interstitial pneumonitis, vasculitis, alopecia, hemolytic anemia, and allergic reactions. Transient rises in BUN and creatinine have occurred with high dose melphalan and also acute renal failure. Tissue necrosis may result if infiltration occurs.

TACROLIMUS (Prograf®, FK506)

AVAILABILITY
Tacrolimus is commercially available as an injection (5 mg/mL; 1 mL ampuls) and as oral capsules (0.5 mg, 1 mg, and 5 mg).

STORAGE & STABILITY
Store tacrolimus capsules and injection at controlled room temperature, 15°C-30°C (59°F-86°F).

PREPARATION – FOR IV USE
Tacrolimus injection must be diluted prior to IV infusion with 0.9% sodium chloride or 5% dextrose injection to a concentration of 4-20 mcg/mL. Solutions should be prepared in non-PVC plastic or glass. Tacrolimus injection and diluted solutions of the drug should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

ADMINISTRATION
Oral therapy should be started as soon as possible as per protocol and 8 to 12 hours after stopping intravenous therapy. Oral doses will be administered twice a day. The conversion from IV to oral therapy should take into account concomitant medications (such as voriconazole).

TOXICITY
In patients receiving tacrolimus, 5% to 47% experienced anemia, 8% to 32% experienced leukocytosis, and 14% to 24% experienced thrombocytopenia. Rare cases of microangiopathic hemolytic anemia have been reported. Chest pain was reported in 19%. Mild to moderate hypertension is a common adverse effect associated with tacrolimus therapy. Antihypertensive therapy may be required. The most common adverse effects of tacrolimus have involved the central nervous system, and include headache (37% to 64%), tremors (48% to 56%), insomnia (32% to 64%), paresthesia (17% to 40%), and dizziness (19%). Tremor and headache may respond to dosage reduction. Visual changes, agitation, anxiety, confusion, seizures, depression, hallucinations, myoclonus, neuropathy, psychosis, incoordination, and abnormal dreams have been reported in 3% to 15%. Hyperkalemia (13% to 45%), hypokalemia (13% to 29%) hypophosphatemia (49%) and hypomagnesemia (16% to 48%) have been associated with tacrolimus therapy. Hyperuricemia has been reported in >3%. Gastrointestinal adverse effects included nausea (32% to 46%), vomiting (14% to 29%), anorexia (7% to 34%), constipation (23% to 35%), and diarrhea (37% to 72%). Nephrotoxicity was reported in 38% to 52% of liver and kidney transplant patients, respectively. Hematuria has been reported in greater than 3%. Abnormal liver function tests have been reported in 6% to 36% of patients; ascites in 7% to 27%.

Other effects reported in clinical trials include pain, fever, asthenia, back pain, and peripheral edema. The incidence of hyperglycemia was 17% and may require therapy with insulin. Other less frequently occurring effects include abscess, chills, peritonitis, and photosensitivity reactions. Anaphylaxis has been reported in a few patients receiving intravenous tacrolimus. Tacrolimus injection contains cremophor which in other drugs has been associated with anaphylaxis. Because tacrolimus is an immunosuppressant, the risk of opportunistic infections is increased.

DRUG INTERACTIONS

Tacrolimus is metabolized by cytochrome P450 3A4. Drugs that are inhibitors (e.g. itraconazole) of inducers (e.g. phenytoin) of 3A4 might be expected to increase or decrease tacrolimus concentrations, respectively, possibly resulting in increased or decreased effects.

ETOPOSIDE

DESCRIPTION

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4'-demethylepipodophyllotoxin 9-[4,6-0-(R)-ethylidene-β-D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.58 and a molecular formula of C29H32O13.

Etoposide Injection USP is administered intravenously. Etoposide Injection USP is available in 100 mg (5 mL) and 250 mg (12.5 mL) sterile, multiple dose vials. The pH of the clear, colourless to pale yellow solution is 3 to 4. Each mL contains 20 mg Etoposide, 2 mg anhydrous citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) dehydrated alcohol. Vial headspace contains nitrogen.

The structural formula is:

CLINICAL PHARMACOLOGY

Its main effect, however, appears to be at the G2 portion of the cell cycle in mammalian cells. The predominant macromolecular effect of Etoposide appears to be the induction of DNA strand breaks by an interaction with DNA topoisomerase II or the formation of free radicals.

PHARMACOKINETICS

On intravenous administration, the disposition of Etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m2 and, like the terminal elimination half-life, are independent of dose over a range of 100 to 600 mg/m2. Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (Cmax) values increase linearly with dose.

Etoposide enters the CSF poorly., Etoposide is highly protein bound (97%) to human plasma proteins.

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There is no evidence of a first-pass effect for EtoposideIn adults, the total body clearance of Etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. Patients with impaired renal function receiving Etoposide have exhibited reduced total body clearance, increased AUC and a lower volume of distribution at steady state.

WARNINGS

Patients being treated with Etoposide Injection USP must be frequently observed for myelosuppression both during and after therapy. Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

For parenteral administration, Etoposide Injection USP should be given only by slow intravenous infusion (usually over a 30- to 60-minute period), since hypotension has been reported as a possible side effectof rapid intravenous injection. Etoposide Injection USP should be considered a potential carcinogen in humans.

ADVERSE REACTIONS

The following data on adverse reactions are based on intravenous administration of Etoposide Injection USP as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

- Hematologic Toxicity
- Myelosuppression. .
- Gastrointestinal Toxicity

- Nausea and vomiting are the major gastrointestinal toxicities. Mild to severe mucositis/esophagitis may occur.
- Hypotension
- Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that Etoposide Injection USP be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to cessation of the infusion administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.
- Allergic ReactionsAnaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous Etoposide Injection USP and in less than 1% of the patients treated with oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of Etoposide Injection USP.
- Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely.
- Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.
- Alopecia, Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

OTHER TOXICITIES
The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation, and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with Etoposide Injection USP. Metabolic acidosis has also been reported in patients receiving higher doses.

Reports of extravasation with swelling have been received postmarketing. Rarely extravasation has been associated with necrosis and venous induration.
The incidences of adverse reactions in the table that follows are derived from multiple databases from studies in 2,081 patients when Etoposide Injection USP was used either orally or by injection as a single agent.

DOSAGE AND ADMINISTRATION
Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with undilutedEtoposide Injection USP.

ADMINISTRATION PRECAUTIONS
As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of Etoposide Injection USP. Skin reactions associated with accidental exposure to Etoposide Injection USP may occur. The use of gloves is recommended. If Etoposide Injection USP solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

PREPARATION FOR INTRAVENOUS ADMINISTRATION
Etoposide Injection USP must be diluted prior to use with either 5% Dextrose Injection, USP, or0.9% Sodium Chloride Injection, USP, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported; hence, it is recommended that the Etoposide Injection USP solution be administered over a 30- to 60-minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. Etoposide Injection USP should not be given by rapid intravenous injection.Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STABILITY
Unopened vials of Etoposide Injection USP are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent light in both glass and plastic containers.
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.1–8 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW IS ETOPOSIDE SUPPLIED
Etoposide Injection USP
NDC 16729-114-31 100 mg/5 mL Sterile, Multiple Dose Vial
NDC 16729-114-32 250 mg/12.5 mL Sterile, Multiple Dose Vial
Store at 20° to 25°C (68° to 77°F). [See USP controlled room temperature].

CYTARABINE
Antimetabolite antineoplastic agent; synthetic pyrimidine antagonist.dfi

ADMINISTRATION
Conventional cytarabine: Administer by rapid IV injection or continuous IV infusion, sub-Q injection, or intrathecal injection; abcj also has been administered by IM injection† and by continuous sub-Q infusion†.f

RECONSTITUTION
Add 5, 10, 10, or 20 mL of bacteriostatic water for injection containing 0.945% benzyl alcohol to a vial containing 100, 500, 1000, or 2000 mg cytarabine powder; resultant solutions contain 20, 50, 100, or 100 mg of cytarabine per mL, respectively. Diluents containing benzyl alcohol should not be used in neonatesfj or in high-dose† regimens. The desired dose of reconstituted solution may be given by rapid IV injection or may be further diluted with 5% dextrose or 0.9% sodium chloride injection for IV infusion.

Dilution Cytarabine injection solution (containing 20 or 100 mg/mL) may be diluted with a compatible IV solution (e.g., 5% dextrose injection, 0.9% sodium chloride injection) for direct IV injection, rapid IV injection, or IV infusion. Cytarabine injection in pharmacy bulk package solution (containing 20 mg/mL) should be diluted with a compatible IV solution (e.g., 5% dextrose injection, 0.9% sodium chloride injection) for IV infusion. Alternatively, desired dose of the solution reconstituted from powder may be further diluted with 5% dextrose or 0.9% sodium chloride injection for IV infusion

RATE OF ADMINISTRATION
Has been given over 1–3 hours when used for treatment of refractory or secondary acute leukemia and refractory non-Hodgkin’s lymphomas.Also administered by rapid IV injection or continuous IV infusion.

RECONSTITUTION
Add 5, 10, 10, or 20 mL of bacteriostatic water for injection containing 0.945% benzyl alcohol to a vial containing 100, 500, 1000, or 2000 mg cytarabine powder; resultant solutions contain 20, 50, 100, or 100 mg of cytarabine per mL, respectively.j
Diluents or drug solutions containing benzyl alcohol should not be used in neonates or in high-dose† regimens.

WARNINGS

Hematologic EffectsConventional cytarabine: Potent myelosuppressant. High-dose Regimens with Conventional Cytarabine

Severe and sometimes fatal CNS, GI, and pulmonary toxicities reported following experimental dosage regimens for refractory or secondary acute leukemia or refractory non-Hodgkin's lymphomas; differ from reactions seen with regimens employing lower dosages.Cerebral and cerebellar dysfunction (e.g., somnolence, coma, personality changes) reported; usually reversible. Reversible, acute aseptic meningitis, combined with cerebellar dysfunction, reported in at least 1 patient.Peripheral motor and sensory neuropathies have occurred occasionally.Patients with renal or hepatic impairment may be at increased risk of CNS toxicity associated with high-dose cytarabine therapy. Monitor patients receiving high-dose therapy closely for signs of central or peripheral neurotoxicity Dosage schedule adjustment may be necessary to avoid irreversible neurologic toxicity. Severe GI ulceration (including pneumatosis cystoides intestinalis leading to peritonitis), bowel necrosis, necrotizing colitis, hepatic abscess or hepatic damage with increased hyperbilirubinemia reported. Pancreatitis reported in patients previously treated with asparaginase and those receiving high-dose cytarabine therapy.Pulmonary edema reported. Diffuse interstitial pneumonitis reported occasionally in patients receiving relatively high doses (e.g., 1 g/m2) of cytarabine alone or in combination with other antineoplastic agents.A syndrome of acute respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly, which was sometimes fatal, has been reported in patients with refractory acute leukemia receiving high-dose therapy.Severe skin rash leading to desquamation has been reported rarely. Complete alopecia occurs more commonly with high-dose regimens.Fatal cardiomyopathy reported in patients receiving high-dose cytarabine in combination with cyclophosphamide in preparation for bone marrow transplantation; this cardiac toxicity may be schedule dependent.Hemorrhagic conjunctivitis and reversible corneal toxicity (e.g., keratitis) reported; may be minimized or Sensitivity Reactions. AnaphylaxisAt least one case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported after IV administration of conventional cytarabine.

GENERAL PRECAUTIONS

- Cytarabine (Ara-C) Syndrome
- Cytarabine syndrome reported; may manifest as fever, myalgia, bone pain, maculopapular rash, conjunctivitis, malaise, and occasionally chest pain..j Generally occurs 6–12 hours after administration of conventional cytarabine..
- Corticosteroids are beneficial in treatment and prevention.If symptoms require treatment, consider administration of corticosteroids, as well as continuation of conventional cytarabine therapy..
- GI Effects
- Nausea and vomiting are more frequent and severe following rapid IV administration of conventional cytarabine than with continuous IV infusion.
- Pancreatitis - Pancreatitis reported in patients receiving conventional cytarabine and in those previously treated with asparaginase..
- Hyperuricemia - Hyperuricemia may occur in patients receiving conventional cytarabine because of extensive purine catabolism accompanying rapid cellular destruction..
- Monitor serum uric acid concentrations in patients receiving conventional cytarabine..Hyperuricemia may be minimized or prevented by adequate hydration, alkalinization of urine, and/or administration of allopurinol.
- Hepatic Impairment, Use with caution; increased risk of CNS toxicity after high-dose therapy with conventional cytarabine because of decreased clearance. Assess hepatic function prior to and periodically during prolonged therapy.
- Renal Impairment, Use with caution; increased risk of CNS toxicity after high-dose therapy with conventional cytarabine because of decreased clearance Assess renal function prior to and periodically during prolonged therapy.

COMMON ADVERSE EFFECTS

- IV, sub-Q, or IM administration of conventional cytarabine: Myelosuppression, anorexia, nausea, vomiting, diarrhea, oral and anal inflammation or ulceration, hepatic dysfunction, fever, rash,

thrombophlebitis, bleeding (all sites).

INTERACTIONS FOR CYTARABINE
No formal drug interaction studies conducted with liposomal cytarabine to date.

PHARMACOKINETICS
AbsorptionBioavailability
Conventional cytarabine: <20% of dose is absorbed after oral administration; not effective when administered orally. Conventional cytarabine: Continuous IV infusions produce relatively constant plasma concentrations of the drug in 8–24 hours.

Distribution Extent
Conventional cytarabine: Rapidly and widely distributed into tissues and fluids, including liver, plasma, and peripheral granulocytes crosses blood-brain barrier to a limited extent.Conventional cytarabine: CSF concentrations are higher during continuous IV or sub-Q infusion than after rapid IV injection and are approximately 40–60% of plasma concentrations.Conventional cytarabine: Apparently crosses placenta;not known if distributed into milk.

Half-life
Conventional cytarabine: After rapid IV injection, plasma drug concentrations appear to decline in a biphasic manner with a half-life of about 10 minutes in the initial distributive phase and about 1–3 hours in the terminal elimination phase; .reportedly undergoes triphasic elimination in some patients..
Conventional or liposomal cytarabine: Liposomal cytarabine has a substantially longer half-life in the CSF than conventional formulations after intrathecal injection.Conventional or liposomal cytarabine: CSF concentrations reportedly decline in a biphasic manner after intrathecal injection.di CSF terminal half-life of conventional cytarabine is approximately 2–3.4 hours;.CSF terminal half-life was 100–263 hours after intrathecal liposomal cytarabine doses ranging from 12.5–75 mg.

Stability Storage
Conventional Cytarabine Powder for Injection25°C (may be exposed to 15–30°C)..
Conventional Cytarabine Injection15–30°C. Store in manufacturer's carton and protect from light.

BCNU (CARMUSTINE)

PHARMACOLOGY
Carmustine alkylates DNA and RNA and also inhibits several enzymes by carbamoylation of amino acids in proteins. Antineoplastic and toxic activities may be caused by metabolites.
Pharmacokinetics

ABSORPTION
IV Vd is 3.25 L/kg. Crosses the blood-brain barrier.

ELIMINATION
The t ½ is 22 min. Cl is 56 mL/min/kg. Approximately 60% is excreted in the urine; 6% is expired as CO 2 .
GENERAL ADVICE
Administer by IV infusion. Follow procedures for proper handling and disposal of chemotherapy drugs. Wear gloves and avoid skin exposure and inhalation of fumes.

The reconstituted solution is administered by IV drip over 1 to 2 h. Shorter infusion times may produce intense pain and burning at the site of injection.Dissolve 1 vial with 3 mL of the dehydrated alcohol diluent, followed by 27 mL of sterile water for injection for a final concentration of 3.3 mg/mL in 10% alcohol. This solution may be further diluted with 5% dextrose for a concentration of 0.2 mg/mL in glass containers.Accidental contact of carmustine with skin can cause temporary severe burning and hyperpigmentation; wear gloves when handling. Double gloving is recommended.

When administered with polyvinyl chloride tubing, longer infusion times may result in unacceptable drug loss. To avoid drug loss, polyethylene tubing, such as nitroglycerin tubing, can be utilized for infusions of carmustine.Open the foil pouches containing the wafer in the operating room immediately prior to implantation.Unopened foil pouches are stable at room temperature for up to 6 h at a time.
Wafers may be used if broken in half. Do not use if broken in more than 2 pieces; dispose of as a hazardous chemical waste.Use a dedicated surgical instrument for handling the wafers during implantation.

STORAGE/STABILITY
Store the unopened vials in a refrigerator (2° to 8°C; 3° to 46°F). After reconstitution, store at room temperature (25°C; 77°F) for up to 8 h. Protect from light.

ADVERSE REACTIONS
- CNS - Depression (16%); intracranial hypertension (9%); anxiety, facial paralysis (7%); ataxia, hypesthesia (6%); dizziness, hallucinations, seizures (5%); headache (28%); meningitis; abscess; asthenia; confusion; somnolence; brain edema; intracranial infection.
- Dermatologic - Rash (wafer) (12%); local burning pain at the injection site; intense flushing of the skin.
- GI - Constipation (19%); abdominal pain, diarrhea (5%), (wafer); nausea (22%); vomiting (21%).
- Genitourinary - UTI (8%; wafer); amenorrhea; male infertility.
- Hematologic - Bone marrow suppression; myelosuppression.
- Hepatic - Transient LFT elevations; hepatic necrosis and veno-occlusive disease after bone marrow transplantation.
- Metabolic - Diabetes mellitus (wafer).
- Renal - Dose-related, delayed-onset, progressive renal failure.
- Respiratory - Early pulmonary toxicity; delayed pulmonary fibrosis.
- Special Senses - Retinitis; optic neuritis; suffusion of the conjunctiva.

WARNINGS
- Bone marrow suppression (notably thrombocytopenia and leukopenia) May contribute to bleeding and infections. Toxicity is cumulative, thus adjust dose based on nadir counts from prior doses. Do not repeat doses more frequently than every 6 wk. Perform weekly complete blood cell counts for 6 wk postdose.
- Hematologic - The most frequent and serious toxic effect of injectable carmustine is delayed myelosuppression.
- Pulmonary fibrosis - Delayed onset pulmonary fibrosis has occurred up to 17 yr after treatment and has been reported in patients who received injectable carmustine in childhood and early adolescence.
- Pulmonary toxicity -Pulmonary toxicity from injectable carmustine appears to be dose-related. Patients receiving more than 1400 mg/m 2 cumulative dose are at significantly higher risk than those receiving less. Other risk factors include history of lung disease and duration of treatment. Cases of fatal pulmonary toxicity have occurred.
- Monitor liver and renal function tests periodically.Conduct baseline pulmonary function studies and frequent pulmonary function tests during treatment. Patients with a baseline less than 70% of predicted forced vital capacity (FVC) or carbon monoxide diffusing capacity (DL co) are at particular risk.
- Long-term use of nitrosoureas has been reported to be associated with the development of secondary malignancies.There have been reports of persistent testicular damage causing infertility with injectable carmustine.
- Nausea and vomiting after IV administration. This dose-related toxicity appears within 2 h of dosing and lasts 4 to 6 h. Healing abnormalities - The majority of these events were mild to moderate in severity.
- Reversible hepatic toxicity, manifested by increased transaminase, alkaline phosphatase, and bilirubin levels, has occurred in a small percentage of patients using injectable carmustine.
- Ocular - Toxicity manifested as nerve fiber-layer infarcts and retinal hemorrhages has been associated with high dose injectable carmustine therapy.

- Renal toxicity - Decrease in kidney size, progressive azotemia, and renal failure have occurred in patients.

ALEMTUZOMAB (CAMPATH)

CAMPATH DOSAGE AND ADMINISTRATION
Premedication and Patient Monitoring
To minimize risk of IV infusion-related reactions, administer diphenhydramine hydrochloride 50 mg and acetaminophen 500–1000 mg 30 minutes prior to first alemtuzumab infusion and when dosage is escalated.1 (See Infusion-related Effects under Cautions.)
Monitor patients carefully during or shortly after infusion for manifestations of infusion reactions (e.g., rigors, fever, bronchospasm, chills, nausea, vomiting, rash, urticaria, dyspnea, hypotension).1

To minimize risk of injection site reactions, administer an antihistamine and acetaminophen prior to sub-Q† injections (e.g., 30 minutes before administration);343536 in one study, premedication was gradually withdrawn following resolution of any injection-related reactions.34

Anti-infective Prophylaxis - To minimize risk of serious opportunistic infections, give prophylactic anti-infectives upon initiation of alemtuzumab and continue for 2 months after completion of therapy or until CD4+ T-cell count ≥200/mm3 (whichever occurs later).1 (See Infectious Complications under Cautions.)
Administer co-trimoxazole (sulfamethoxazole 800 mg and trimethoprim 160 mg per dose) twice daily 3 times weekly (or equivalent) for prophylaxis of Pneumocystis jiroveci (formerly P. carinii) pneumonia.1
Administer famciclovir 250 mg twice daily (or equivalent) for prophylaxis of herpesvirus infection.1

ADMINISTRATION
Administer by IV infusion.1 May be administered by sub-Q injection†.IV Administration
For solution compatibility information, see Compatibility under Stability.Administer by IV infusion only.1 Do not administer by rapid IV injection (e.g., IV push or bolus). Do not mix with any other drug or administer any other drug simultaneously in the same IV line. Vials are for single use only.

DILUTION
Use strict aseptic technique since drug product contains no preservative. Do not shake vial prior to use.15
Withdraw appropriate dose of alemtuzumab concentrate into a syringe calibrated in increments of 0.01 mL when preparing a 3-mg dose or a 10-mg dose; for a 30-mg dose, use a syringe calibrated in increments of 0.1 mL.1 To prepare a 3-mg dose, withdraw 0.1 mL of alemtuzumab concentrate into a 1-mL syringe; to prepare a 10-mg dose, withdraw 0.33 mL into a 1-mL syringe; and to prepare a 30-mg dose, withdraw 1 mL into either a 1- or 3-mL syringe.1 Discard vial, including any unused portion, after withdrawal of dose.1
Add appropriate dose of alemtuzumab concentrate to 100 mL of 0.9% sodium chloride or 5% dextrose injection; gently invert bag to mix solution.1

RATE OF ADMINISTRATION
Administer dose over 2 hours. Hematologic Toxicities - Adjust dosage and/or temporarily discontinue therapy if severe cytopenias (except lymphopenia) occur; permanently discontinue drug in patients with evidence of autoimmune hematologic toxicity (i.e., autoimmune anemia or thrombocytopenia).
No dosage modifications recommended for lymphopenia.

INFUSION REACTIONS
Withhold therapy in patients experiencing grade 3 or 4 infusion reactions.
Infectious Complications - If serious infection occurs, temporarily discontinue therapy; may reinitiate therapy following resolution of infection. Withhold therapy during antiviral therapy for CMV infection or confirmed CMV viremia (defined as positive for CMV according to PCR in ≥2 consecutive samples obtained ≥1 week apart) and initiate anti-infective therapy (ganciclovir or equivalent).

CONTRAINDICATIONS
None.

WARNINGS/PRECAUTIONS
Use under supervision of a qualified clinician experienced in therapy with antineoplastic agents.

- Hematologic Effects
- Risk of severe (sometimes fatal) autoimmune anemia, autoimmune thrombocytopenia, and prolonged myelosuppression.
- Hemolytic anemia, pure red cell aplasia, bone marrow aplasia, and hypoplasia have occurred in patients receiving recommended dosage.1 Increased incidence of pancytopenia with higher than recommended dosages (i.e., single doses >30 mg or cumulative weekly doses >90 mg).
- Withhold alemtuzumab in patients who develop severe cytopenias (except lymphopenia).1 (See Dosage under Dosage and Administration.)
- Discontinue therapy permanently in patients with autoimmune hematologic toxicity (i.e., autoimmune anemia or thrombocytopenia) or recurrent or persistent severe cytopenias (except lymphopenia).1 Safety of reinitiating alemtuzumab in patients with autoimmune cytopenia or bone marrow aplasia not established.
- Severe idiopathic thrombocytopenic purpura (ITP), sometimes fatal, reported in 3 patients receiving alemtuzumab in a clinical trial evaluating the drug for treatment of multiple sclerosis.32 Two of these patients received cumulative doses that exceeded the cumulative weekly dose limit.
- Infusion Reactions - Risk of acute infusion reactions, including rigors, fever, bronchospasm, chills, nausea, vomiting, rash, urticaria, dyspnea, and hypotension occurring during or shortly after IV infusion, particularly during first week of therapy.
- Serious, sometimes fatal, infusion-related reactions (e.g., syncope, pulmonary infiltrates, ARDS, respiratory arrest, cardiac arrhythmias, MI, acute cardiac insufficiency, cardiac arrest, angioedema, anaphylactoid shock) reported. Monitor closely for adverse reactions during and shortly after infusion.1 Withhold alemtuzumab in patients experiencing grade 3 or 4 infusion reactions.1 Initiate medical management (e.g., glucocorticoids, epinephrine, meperidine) as clinically indicated.
- Premedication and incremental dosage escalation used to prevent or ameliorate reactions.
  Acute systemic injection-related reactions, including fever and chills/rigors, also reported with sub-Q† injection of alemtuzumab, but appear to be more common with IV infusion
  Immunosuppression
  Risk of severe and profound lymphopenia, which increases the potential for tranfusion-associated graft versus host disease (TA-GVHD).12 Administer only irradiated blood products unless immediate transfusion is required because of emergency.1
  Infectious Complications -Risk of serious (sometimes fatal) opportunistic bacterial, viral, fungal, or protozoan infections resulting from severe and profound lymphopenia.1
- Administer prophylactic anti-infectives against Pneumocystis jiroveci (formerly Pneumocystis carinii) and herpesvirus infections during alemtuzumab therapy and for at least 2 months after the last dose of alemtuzumab.134 (See Anti-infective Prophylaxis under Dosage and Administration.)
- Risk of potentially serious or life-threatening CMV infection.1 Monitor patient closely for CMV infection during and for at least 2 months following completion of alemtuzumab therapy.1

If serious infection occurs, temporarily discontinue alemtuzumab;1 reinitiate therapy following resolution of infection.

FLUDARABINE (Fludara)

AVAILABILITY
Fludarabine is commercially available as a white, lyophilized powder. Each vial contains 50 mg of fludarabine, 50 mg of mannitol and sodium hydroxide to adjust pH.

STORAGE & STABILITY
Intact vials should be stored under refrigeration. Reconstituted vials are stable for 16 days at room temperature or under refrigeration. Solutions diluted in D5W or NS are stable for 48 hours at room temperature or under refrigeration.

PREPARATION
Fludarabine should be reconstituted with Sterile Water for Injection, USP or normal saline per institutional pharmacy guidelines.

ADMINISTRATION
Fludarabine will be administered as an IV infusion over 30 minutes.

TOXICITY
Myelosuppression, (dose-limiting toxicity), fever, mild nausea and/or vomiting, diarrhea, stomatitis, skin rashes, myalgia, headache, agitation, hearing loss, transient episodes of somnolence and fatigue, autoimmune hemolytic anemia (may be life-threatening), peripheral neuropathy, and pulmonary toxicity. (Both pneumonia and hypersensitivity reactions have been reported. Fatal pulmonary toxicity has been described, especially when fludarabine was used in combination with pentostatin. Severe, fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status was encountered almost exclusively after very high doses of fludarabine. Such toxicity has only been rarely demonstrated at the 25-30 mg /m2 dosage of fludarabine. Very rarely described complications include transfusion-associated graft versus host disease. Tumorlysis syndrome has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed.

MYCOPHENOLATE MOFETIL (CellceptÒ; MyforticÒ; MMF)

AVAILABILITY
Mycophenolatemofetil is available as a Capsule, as mofetil: CellCept®: 250 mg;
as Injection, powder for reconstitution, as mofetil hydrochloride: CellCept®: 500 mg [contains polysorbate 80]; as Powder for oral suspension, as mofetil: CellCept®: 200 mg/mL (225 mL) [provides 175 mL suspension following reconstitution; contains phenylalanine 0.56 mg/mL; mixed fruit flavor]; as a Tablet, as mofetil: CellCept®: 500 mg [may contain ethyl alcohol]; and as a Tablet, delayed release, as mycophenolic acid: Myfortic®: 180 mg, 360 mg [formulated as a sodium salt].

STORAGE & STABILITY
Intact vials should be stored at room temperature 15ºC to 30ºC (59ºF to 86ºF). Store solutions at 15ºC to 30ºC (59ºF to 86ºF) and begin infusion within 4 hours of reconstitution. Store capsules at room temperature of 15ºC to 39ºC (59ºF to 86ºF). Tablets should be stored at room temperature of 15ºC to 39ºC (59ºF to 86ºF) and protected from light. Store powder for oral suspension at room temperature of 15ºC to 39ºC (59ºF to 86ºF). Once reconstituted, the oral solution may be stored at room temperature or under refrigeration. Do not freeze. The mixed suspension is stable for 60 days.

PREPARATION
Mycophenolatemofetil is stable in D5W should be reconstituted per institutional pharmacy guidelines.

ADMINISTRATION
Intravenous solutions of mycophenolatemofetil should be administered over at least 2 hours (either peripheral or central vein); do not administer intravenous solution by rapid or bolus injection. Oral dosage formulations (tablet, capsule, suspension) should be administered on an empty stomach to avoid variability in MPA absorption. The oral solution may be administered via a nasogastric tube (minimum 8 French, 1.7 mm interior diameter); oral suspension should not be mixed with other medications. Delayed release tablets should not be crushed, cut, or chewed.

TOXICITY
Pain, abdominal pain, fever, headache, infection, sepsis, asthenia, chest pain, back pain, hypertension, tremor, insomnia, dizziness, acne, rash, diarrhea, constipation, mild N/V, oral monoliasis, anemia, leukopenia, thrombocytopenia, hypochromic anemia, leukocytosis, peripheral edema, hypercholesterolemia, hypophosphatemia, edema, hypo or hyperkalemia, hyperglycemia, infection, dyspnea, cough increase, pharyngitis, bronchitis, pneumonia, UTI, hematuria, kidney tubular necrosis, urinary tract disorder.

RABBIT ANTITHYMOCYTE GLOBULIN(ThymoglobulinÒ, rATG)

AVAILABILITY
Antithymocyte globulin is commercially available. Each package contains two vials: the first vial contains 25 mg antithymocyte globulin, and the second vial contains > 5 mL SWFI diluent.

STORAGE & STABILITY
Ampuls must be refrigerated (2oC-8oC/ 36oF-46oF),). Do not freeze.

PREPARATION
Reconstitute 25 mg vial with diluent provided by manufacturer (SWFI > 5 mL). Roll vial gently to dissolve powder. Use contents of vial within 4 hours of reconstitution. Dilute dosage to a final concentration of 0.5 mg/mL in 0.9% sodium chloride injection or 5% dextrose injection. Gently invert admixture 1-2 times to mix solution. Use admixture solution immediately. Final concentration must be 0.5 mg/mL.

ADMINISTRATION
Infuse the first dose over at least six hours, and subsequent doses over at least 4 hours. Infuse through a 0.22 micron in-line filter into a high-flow vein. Premedications include acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO/IV, and methylprednisolone 1 mg/kg (at the initiation and half-way through antithymocyte globulin administration).

TOXICITY
Infusion-related toxicities, including fevers, chills, rash, dyspnea, cardiovascular (hypo- or hypertension, tachycardia, edema, chest pain). In rare cases, anaphylaxis has been reported in which case the infusion should be terminated immediately, and emergency treatment with epinephrine and other resuscitative measures should be instituted. rATG should not be administered again to this patient.
Immunosuppression is a common feature of rATG and can result in severe infections including sepsis, CMV, and urinary tract infections. Serum sickness, neutropenia (57%), thrombocytopenia (37%), leucopenia (57%), pain (46%), headache (40%), nausea and diarrhea (37%), peripheral edema (34%), systemic infection, malaise, pain, stomatitis, GI bleed, swelling or redness at injection site, myalgia, back pain, development of human anti-rabbit antibodies (HARA).

Neulasta (Pegfilgrastim)

INDICATIONS AND USAGE
Neulasta is a leukocyte growth factor indicated to:
 Decrease the incidence of infection, as manifested by febrileneutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinicallysignificant incidence of febrile neutropenia.
 Increase survival in patients acutely exposed to myelosuppressive dosesof radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).
Neulasta is not indicated for the mobilization of peripheral blood progenitorcells for hematopoietic stem cell transplantation.

DOSAGE AND ADMINISTRATION
 Patients with cancer receiving myelosuppressive chemotherapy
    - o 6 mg administered subcutaneously once per chemotherapy cycle.
    - o Do not administer between 14 days before and 24 hours afteradministration of cytotoxic chemotherapy.
    - o Use weight based dosing for pediatric patients weighing less than45 kg
 Patients acutely exposed to myelosuppressive doses of radiation
    - o Two doses, 6 mg each, administered subcutaneously one weekapart. Administer the first dose as soon as possible after suspectedor confirmed exposure to myelosuppressive doses of radiation, anda second dose one week after
    - o Use weight based dosing for pediatric patients weighing less than 45 kg

DOSAGE FORMS AND STRENGTHS Injection: 6 mg/0.6 mL solution in a single-use prefilled syringe formanual use only Injection: 6 mg/0.6 mL solution in a single prefilled syringe co-packagedwith the On-body Injector for Neulasta

CONTRAINDICATIONS
Patients with a history of serious allergic reactions to human granulocytecolony-stimulating factors such as pegfilgrastim or filgrastim

WARNINGS AND PRECAUTIONS
 Fatal splenic rupture: Evaluate patients who report left upper abdominalor shoulder pain for an enlarged spleen or splenic rupture
 Acute respiratory distress syndrome (ARDS): Evaluate patients whodevelop fever, lung infiltrates, or respiratory distress. DiscontinueNeulasta in patients with ARDS
 Serious allergic reactions, including anaphylaxis: Permanentlydiscontinue Neulasta in patients with serious allergic reactions
 The On-body Injector for Neulasta uses acrylic adhesive. For patientswho have reactions to acrylic adhesives, use of this product may result in a significant reaction
 Fatal sickle cell crises: Have occurred
 Glomerulonephritis: Evaluate and consider dose-reduction orinterruption of Neulasta if causality is likely

ADVERSE REACTIONS
Most common adverse reactions (≥ 5% difference in incidence compared toplacebo) are bone pain and pain in extremity

APPENDIX E

ACUTE GRAFT VERSUS HOST DISEASE GRADING

Consensus grading of acute GVHD[7]

	Organ/Extent of Involvement		
	Skin	**Liver**	**Intestinal Tract**
Stage			
1	Rash on <25% of skin–	Bilirubin 2–3 mg/dL‡	Diarrhea >500 mL/d or persistent nausea§
2	Rash on 25–50% of skin	Bilirubin 3–6 mg/dL	Diarrhea >1,000 mL/d
3	Rash on >50% of skin	Bilirubin 6–15 mg/dL	Diarrhea >1,500 mL/d
4	Generalized erythroderma with bulla formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade			
0	None	None	None
I	Stage 1–2	None	None
II	Stage 3	or Stage 1	or Stage 1
III	—	Stage 2–3	or Stage 2–4
IV¶	Stage 4	or Stage 4	—

Use the “rule of nines” to determine body surface area involvement.

†Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

§Persistent nausea with histologic evidence of GVHD in the stomach or duodenum

yes	platform+medline	author	author		

Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED; 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995; 15:825-8.

APPENDIX F

CHRONIC GRAFT VERSUS HOST DISEASE GRADING

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report	Alexandra H. Filipovich, Daniel Weisdorf, Steven Pavletic, Gerard Socie, John R. Wingard, Stephanie J. Lee, Paul Martin, Jason Chien, Donna Przepiorka, Daniel Couriel, Edward W. Cowen, Patricia Dinndorf, Ann Farrell, Robert Hartzman, Jean Henslee-Downey, David Jacobsohn, George McDonald, Barbara Mittleman, J. Douglas Rizzo, Michael Robinson, Mark Schubert, Kirk Schultz, Howard Shulman, Maria Turner, Georgia Vogelsang, Mary E.D. Flowers	Biology of Blood and Marrow Transplantation - December 2005 (Vol. 11, Issue 12, Pages 945-956, DOI: 10.1016/j.bbmt.2005.09.004)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS[†] **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

OTHERS: Specify:_____

Organ scoring of chronic GVHD. *AP may be elevated in growing children, and not reflective of liver dysfunction. †Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO is not available, grading using FEV1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established [29]. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; <40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12. GVHD indicates graft versus host disease; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see below), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites). Moderate chronic GVHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GVHD. Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

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