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CANCER AND LEUKEMIA GROUP B

CALGB 100103/BMT CTN 0502

A PHASE II STUDY OF ALLOGENEIC TRANSPLANT FOR OLDER PATIENTS WITH AML IN FIRST MORPHOLOGIC COMPLETE REMISSION USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN

Limited Access Study: CALGB- and BMT CTN-Approved Allogeneic Transplant Centers

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A PHASE II STUDY OF ALLOGENEIC TRANSPLANT FOR OLDER PATIENTS WITH AML IN FIRST MORPHOLOGIC COMPLETE REMISSION USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN

SCHEMA PAGE 1 OF 2

Patient Eligibility (see Section 4.0)

Patients with acute myeloid leukemia (AML) (excluding FAB M3) who have achieved a first morphologic complete response and who meet all of the following criteria:

- Complete response (CR) as defined in Section 4.1.1;
- CR was achieved after no more than two cycles of induction chemotherapy with standard cytotoxic chemotherapy (e.g., cytarabine and an anthracycline) or after no more than four cycles of a hypomethylating agent containing regimen including either 5-azacytidine or decitabine;
- Patients may have received as many as but no more than two cycles of consolidation therapy prior to transplant. Any consolidation regimen that does not require transplant may be used. No more than six months can elapse from attainment of morphologically documented CR to transplant on this study.

≥ 4 weeks since prior chemotherapy, radiation or surgery.

Age ≥ 60 years and < 75 years.

Identification of Suitable Donor (see Section 5.0).

Performance Status 0-2

DLCO > 40% with no symptomatic pulmonary disease.

LVEF by ECHO or MUGA ≥ 30%

No uncontrolled diabetes mellitus or serious infection requiring antibiotics.

No known hypersensitivity to E.coli-derived products.

No HIV disease (see Section 4.10)

Initial Required Laboratory Values

Calculated Creatinine Clearance	≥ 40 cc/min
Bilirubin*	< 2 mg/dL
AST	< 3 x ULN

**if bilirubin is 2-3 mg/dL but direct bilirubin is normal patient is eligible.*

Donor Eligibility Criteria (see Sec. 5.0)

The donor may be an HLA-identical sibling (6/6) by serologic typing (A, B, DR) or low resolution molecular HLA tests or a 10/10 locus matched unrelated donor using high resolution DNA-based typing.

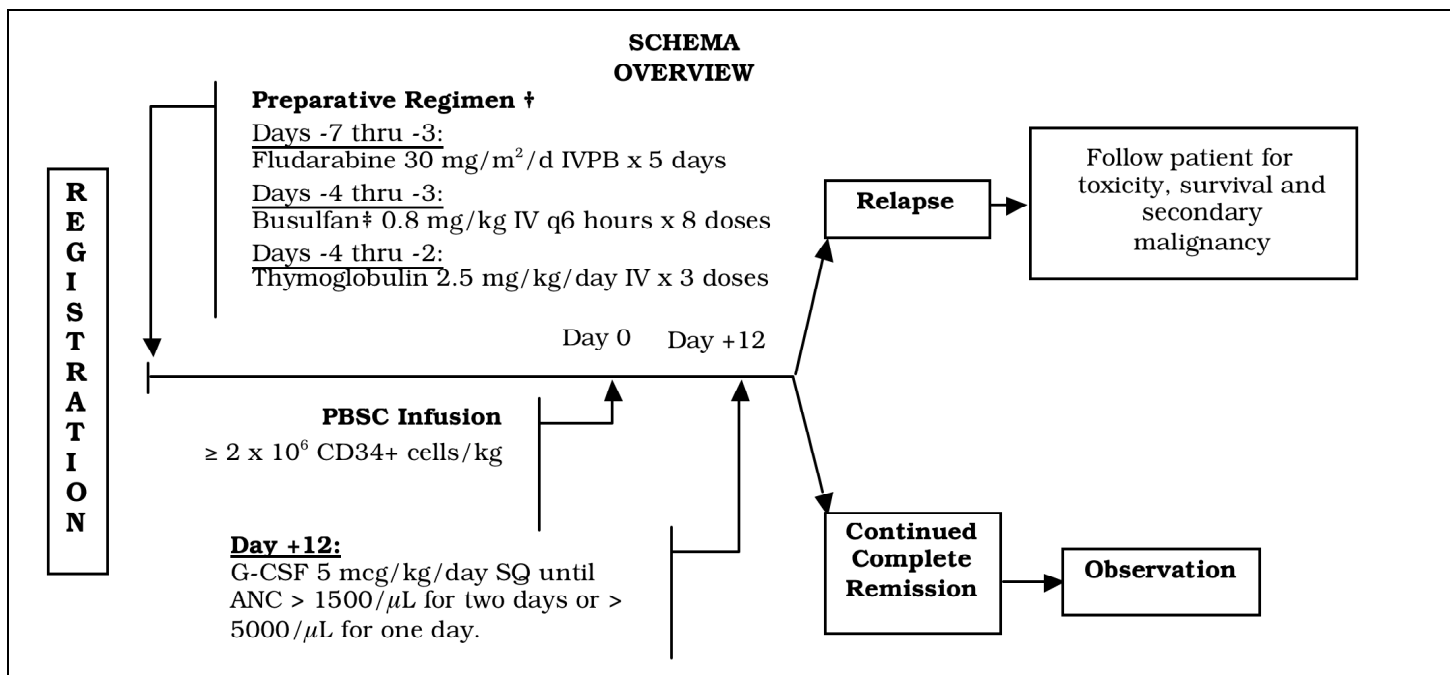
The donor must be healthy and must be an acceptable donor as per institutional standards for marrow or stem cell donation.

No significant cardiopulmonary, renal, endocrine, or hepatic disease.

There is no donor age restriction, if donor is a matched sibling.

Syngeneic donors will not be eligible.

All therapy (including methotrexate and tacrolimus) and growth factor doses are to be based on corrected weight (see Section 9.4)



† See Section 8.2 for supportive care guidelines.

A PHASE II STUDY OF ALLOGENEIC TRANSPLANT FOR OLDER PATIENTS WITH AML IN FIRST MORPHOLOGIC COMPLETE REMISSION USING A NON-MYELOABLATIVE PREPARATIVE REGIMEN

TREATMENT SCHEMA
Schema Page 2 of 2

Patient Preparative Regimen & Stem Cell Infusion (see Sections 8.1, 8.2, & 8.4)

Prior to initiating therapy, placement of a multi-lumen, indwelling Silastic catheter is required.

	F →																			
		B →																		
		ATG →																		
		Antiviral Prophylaxis— in patients with a history of herpes simplex to Day +100 →																		
		T — begin taper between Day +90 - +120 to stop between Day +150 - +180→																		
		PB SCT																		
									M										M	
		Antifungal Prophylaxis ————— through Day +100 —————→																		
																				G-CSF
	PCP prophylaxis through Day +100 (see below).																			
Day	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12

- F** Fludarabine 30 mg/m²/day IVPB over 30 minutes x 5 days on Days -7 through -3.
- B** Busulfan 0.8 mg/kg IV over 2 hours q 6 hours x 8 doses on Days -4 and -3.
- ATG** Rabbit antithymocyte globulin (thymoglobulin) 2.5 mg/kg/day IV over 6 hours x 3 doses on Days -4 through -2. After the first dose, thymoglobulin may be administered over 4 hours. See Section 8.2.1.3 for premedication instructions.
- Antiviral Prophylaxis** Antiviral prophylaxis will occur through Day +100 according to institutional guidelines for patients with a history of herpes simplex infection or seropositivity. Prophylaxis may be extended beyond Day +100 at the discretion of the treating physician. See Section 8.2.2.
- PCP Prophylaxis** PCP prophylaxis will occur through Day +100 according to institutional guidelines. See Section 8.2.4. In patients who develop chronic GVHD, PCP prophylaxis should be extended at the discretion of the physician.
- T** Tacrolimus target serum levels are 5-10 ng/mL. Serum levels are not to exceed 15 ng/mL. The suggested starting dose is 0.03 mg/kg PO BID beginning on Day -2. Begin tapering between Day +90 to +120 with a goal of stopping by Day +150 to +180 (see Section 8.2.1.1).
- PB SCT** Peripheral Blood Stem Cell Transplant. On Day 0 a minimum **total** CD34+ cell dose of 2 x 10⁶/kg (actual weight - recipient) will be infused.
- M** Methotrexate 5 mg/m²/day IV on Days +1, +3, +6 and +11. Hydrate intravenously and induce diuresis (see Section 8.2.1.2).
- Antifungal Prophylaxis** Antifungal prophylaxis will occur according to institutional guidelines through Day +100. See Section 8.2.3.
- G-CSF** Recipients will receive 5 mcg/kg G-CSF SQ daily beginning on Day +12 and continuing until ANC > 1500/μL for two consecutive days or > 5000/μL for one day. If ANC decreases to < 1000/μL then resume G-CSF at 5 mcg/kg/day.

HLA-Identical Sibling Donor Stem Cell Collection (see Section 8.3)

		G-CSF— see below→																		
							Donor Pheresis													
Day	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8				

- G-CSF** Donors will receive 10 mcg/kg SQ on Days -5 through -2 (and, if necessary -1).
- Donor Pheresis** On Days -1 (and 0) donors will undergo leukapheresis for 1-2 days to achieve a CD34+ cell dose of ≥ 2 x 10⁶/kg (actual weight - recipient). If the yield of CD34+ cells is < 2 x 10⁶/kg on Day -1, an additional pheresis will be performed on Day 0. If after two pheresis procedures the total CD34+ cell dose is at least 2.0 x 10⁶/kg, no further pheresis is required. Target CD34+ cell doses will be based on institutional standards, as long as minimum of 2 x 10⁶/kg is achieved. There is no maximum CD34+ cell dose.

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1.0 INTRODUCTION

1.1 Background & Rationale

Less than 20% of patients who are ≥ 60 years of age with acute myeloid leukemia (AML) in first complete remission (CR1) achieve 3-year disease-free survival (DFS) with standard chemotherapy [1]. For 276 patients age 60-75 years who achieved CR on CALGB trials 8525 and 8923 and were randomized to post-remission therapy, the probability of 2- and 3-year DFS were $0.24 \pm .05$ and $0.17 \pm .04$, respectively. The poor outcome of treatment among older patients is the result of increased treatment related mortality, reduced dose intensity due to excess morbidity and the inherent resistance of leukemia among older adults. Treatment resistance is the result of adverse risk factors such as preceding myelodysplasia (MDS) and adverse cytogenetics [2, 3]. Even when these factors are taken into account, relapse risk is independently associated with advanced age [4].

Prospective trials have shown that relapse risk following allogeneic transplantation in first CR is lower than that which follows conventional chemotherapy or autologous transplant [5, 6]. In particular, among patients with high-risk cytogenetics, DFS appears to be improved for those who receive allogeneic transplant in first CR [7]. Therefore, early allogeneic transplant could improve outcome for AML patients ≥ 60 years of age. However, concern regarding excess transplant related mortality (TRM) has generally prevented inclusion of patients ≥ 60 years of age in trials of allogeneic transplant.

With conventional myeloablative preparative regimens, most trials have reported an association of age with TRM, particularly among patients greater than 40-50 years of age [8, 9]. However, there has been very little experience with patients who are over 60. TRM is also related to disease stage so that the effect of age on outcome may be less pronounced among patients with early stage disease (CML in chronic phase or acute leukemia in remission). Rapoport et al. found no effect of age on TRM among 92 patients, most of whom were transplanted for acute leukemia in remission or CML in chronic phase [10]. Similarly, Appelbaum reported excellent results for 33 patients with CML in stable phase who were age 50-60 years [11]. Undoubtedly, recent advances in supportive care have also contributed to the favorable results of transplantation reported in these studies.

New approaches that promise to further reduce TRM include the use of allogeneic peripheral blood stem cells (PBSC) and the use of lower intensity preparative regimens. Allogeneic PBSC transplant is associated with more rapid recovery of both neutrophils and platelets and a recent report from the IBMTR/EBMT noted a significant reduction in TRM with PBSC compared with bone marrow among patients transplanted for advanced leukemia [12-14]. Recognition of the key role played by the graft-vs-tumor effect in elimination of malignancy has led to the recent exploration of non-myeloablative preparative regimens. In the setting of matched sibling donor transplants using fludarabine-based regimens, the vast majority of patients have achieved durable engraftment. Most trials have recruited older patients and those with medical problems that increase the risk of TRM with conventional preparative regimens. Despite this, TRM has generally been comparable to or less than that reported with conventional preparative regimens indicating that this approach may reduce TRM among older patients [15-18]. However, interpretation of results is difficult since most reports have included patients with a variety of diagnosis and disease stages. Shimoni et al. reported on 78 patients with AML (64 pts) or MDS who received fludarabine based preparative regimens followed by allogeneic transplant [19]. With a median follow-up of 20 months, three year survival for good-risk patients was 74%, a result which is particularly encouraging given that two-thirds of the patients were age 55 years or above. Rezvani et al. reported data from the EBMT on 149 patients with acute leukemia or MDS who underwent non-

myeloablative transplant, mostly using fludarabine-based preparative regimens [20]. Median age was 51 years with the oldest patient being 68 years. Among patients with AML in CR1 or CR2, 1 year TRM was only 17% with actuarial relapse risk being 21% and overall survival being 67%. Sayer et al. reported on 117 patients with AML who received allogeneic transplant with non-myeloablative conditioning (fludarabine/busulfan) due to advanced age (31%) or other medical problems that were felt to represent contraindications to treatment with conventional preparative regimens [21]. Median age was 51 years (range of 16-67). At a median observation time of 305 days, the probability of progression-free survival for patients in CR1 was 51% with TRM for all patients being 24%. This relatively low value for TRM is particularly encouraging given that only 44% of these patients were transplanted from HLA-identical family donors.

Recent studies suggest that current supportive care approaches including the use of reduced intensity conditioning regimens, tacrolimus-based GVHD prophylaxis, peripheral blood stem cells, and high resolution DNA-based HLA-typing have mitigated any differences in the risk of TRM when comparing matched unrelated donor transplants to those performed using HLA-matched sibling allografts. The Seattle dataset are the largest, with 303 patients transplanted from matched siblings and 148 recipients of unrelated donor allografts showing an identical one-year TRM of 22% in both groups (Brenda Sandmeier, personal communication). Unrelated donor matching at 10/10 alleles was required for these identical outcomes. The Dana Farber group has transplanted 49 patient using a fludarabine and busulfan-based regimen and preliminarily there does not appear to be a significant difference in TRM (25% overall) between recipients of matched sibling and unrelated donor allografts (Ted Alyea, personal communication). Finally, the MD Anderson group has also demonstrated the feasibility of performing reduced intensity transplants in older patients with myeloid malignancies (23). In summary, despite focusing on older patients and those with significant co-morbidity, non-myeloablative regimens have been associated with relatively low TRM. Following both HLA-identical sibling transplants and volunteer unrelated donor transplants, durable engraftment has been the rule with no apparent increase in relapse risk among patients with low risk disease. Based on the preliminary results discussed above, we propose a trial in which patients age 60 or above with AML in CR1 will receive busulfan/fludarabine and ATG, followed by G-CSF mobilized PBSC collected from an HLA-identical sibling or a well-matched unrelated donor. The primary goal is to determine if this regimen improves DFS compared with conventional chemotherapy.

1.2 Busulfan Pharmacokinetics in Elderly Leukemic Patients

The preparative regimen being used in CALGB 100103 involves a combination of fludarabine and busulfan. Busulfan has established itself as an important component of the preparative regimen for hematopoietic cell transplantation, particularly for the treatment of myeloid malignancies. When oral busulfan has been used in the past, there has been wide interpatient variability in the busulfan areas under the curve achieved. Moreover, high area under the curve (> 1,500) has been correlated with a high risk of fatal venoocclusive disease of the liver, especially in the context of allogeneic transplantation. Based on this observation, many groups have moved to monitoring the pharmacokinetics of busulfan and adjusting the dose to keep the area under the curve within a desired range. The development of IV busulfan has been a significant advance in that the pharmacokinetics of that preparation is much more reliable than with the oral formulation. Nevertheless, there remains significant interpatient variability in the pharmacokinetics of IV busulfan. Although most of the focus on busulfan pharmacokinetics and dose adjustment has been on the relationship between high area under the curve and toxicity, it is likely that lower area under the curves are equally undesirable. In view of the reticence to employ hematopoietic transplantation in elderly patients, the majority of pharmacokinetic studies of busulfan have involved patients under the age of 60. CALGB 100103 represents an ideal setting in which to evaluate the

pharmacokinetics of high-dose busulfan therapy in a population of elderly patients and to compare the pharmacokinetics in such patients with the pharmacokinetics of busulfan previously defined in a younger patient population. In view of the documented pharmacokinetic/pharmacodynamic relationships between busulfan-related toxicity and, possibly, reduced efficacy, pharmacokinetic studies of busulfan in the elderly are of obvious importance.

Plasma busulfan concentrations will be determined with a validated LC/mass spec method developed at the University of Pittsburgh Cancer Institute. Plasma concentrations-versus-time data will be analyzed using non-compartmental methods. Clearance will be determined from the definition: clearance = dose/area under the curve.

1.3 Inclusion of Women and Minorities

Patients who meet eligibility criteria will be included on this study without regard to gender, race, or ethnicity. Gender will be analyzed as a covariate in reporting the results, as will race and ethnicity.

2.0 OBJECTIVES

2.1 Primary Objective

Among patients with AML in CR1 who are ≥ 60 years of age, to determine if allogeneic transplant from a matched sibling or unrelated donor using a non-myeloablative preparative regimen results in 2-year DFS that is better than historical results using standard chemotherapy.

2.2 Secondary Objectives

- 2.2.1 To determine 2-year actuarial risks of transplant-related mortality, acute and chronic GVHD and relapse among patients with AML in CR1 following a non-myeloablative preparative regimen.
- 2.2.2 To examine recovery of T and B cell number and function following non-myeloablative stem cell transplant.
- 2.2.3 To examine the time course of T, B and myeloid progenitor chimerism following this preparative regimen.
- 2.2.4 To characterize the pharmacokinetics of intravenous busulfan used in a non-myeloablative preparation regimen in AML patients age ≥ 60 years.

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. **To maximize patient safety, patients will be treated on this protocol only at CALGB- and Blood and Marrow Transplant Clinical Trial Network-approved allogeneic transplant centers.** Physicians should consider the risks and benefits of any therapy and, therefore, only enroll patients for which the agents administered are appropriate. **Although they will not be considered as formal eligibility criteria, as part of this decision making process, physicians should recognize that the following may increase the risk to the patient entering this protocol:**

- Other serious illnesses which would limit survival to less than two years, or psychiatric conditions which would prevent compliance with treatment or informed consent.
- Uncontrolled or severe cardiovascular disease, pulmonary disease, or infection, which in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.

4.0 ELIGIBILITY CRITERIA

4.1 Patients with acute myeloid leukemia (AML) (excluding FAB M3) who have achieved a first morphologic complete remission and who meet the criteria below. Patients with preceding MDS or treatment-related AML are eligible. Patients with prior CNS involvement are eligible as long as disease is in remission at transplant. Patients with acute leukemia following blast transformation of prior CML or other myeloproliferative disease are excluded.

4.1.1 Complete remission (CR) will be defined according to the revised recommendations of the International Working Group (24) as all of the following:

- Normal bone marrow morphology with < 5% blasts;
- ANC > 1000/ μ L, referring to the count needed to confirm that the patient achieved a CR;
- platelet count > 100,000/ μ L;
- No extramedullary leukemia;
- No blasts in peripheral blood.

4.1.2 CR was achieved after no more than two cycles of induction chemotherapy with standard cytotoxic chemotherapy (e.g., cytarabine and an anthracycline) or after no more than four cycles of a hypomethylating agent containing regimen including either 5-azacytidine or decitabine.

4.1.3 Patients may have received as many as but no more than two cycles of consolidation therapy prior to transplant. Any consolidation regimen that does not require transplant can be used. No more than 6 months can elapse from documentation of morphologic CR to transplant.

4.2 Identification of Hematopoietic Cell Donor

The donor must meet eligibility criteria outlined in Section 5.0.

4.3 \geq 4 weeks since prior chemotherapy, radiation therapy, and surgery.

4.4 Age \geq 60 years and < 75 years.

4.5 Performance Status 0-2.

4.6 DLCO > 40% with no symptomatic pulmonary disease.

4.7 LVEF by ECHO or MUGA \geq 30%.

4.8 No uncontrolled diabetes mellitus or active serious infection requiring antibiotics.

4.9 No known hypersensitivity to E.coli-derived products.

4.10 No HIV infection. Patients with immune dysfunction are at a significantly higher risk of toxicities from intensive immunosuppressive therapies.

4.11 Initial Required Laboratory Data

Calculated Creatinine Clearance	≥ 40 cc/min
Bilirubin*	< 2 mg/dL
AST	< 3 x upper limit of normal.

* If bilirubin is 2-3 mg/dL, but direct bilirubin is normal then patient will be considered eligible.

Institutional normal laboratory values must be recorded on flow sheets.

5.0 DONOR ELIGIBILITY CRITERIA

5.1 Eligible Donor Categories

The following categories of donors will be eligible:

5.1.1 HLA-Identical Sibling (6/6): The donor must be determined to be an HLA-identical sibling (6/6) by serologic typing for class (A, B) and low resolution molecular typing for class II (DRB1).

5.1.1 Matched Unrelated Donor (10/10): High resolution molecular typing at the following loci is required: HLA-A, -B, -C, -DRB1, and -DQB1.

5.2 The donor must be healthy and must be an acceptable donor as per institutional standards for stem cell donation.

5.3 The donor must have no significant cardiopulmonary, renal, endocrine, or hepatic disease.

5.4 There is no donor age restriction if the donor is a matched sibling.

5.5 Syngeneic donors are not eligible.

6.0 REGISTRATION, DATA SUBMISSION, AND CHIMERISM ANALYSIS

6.1 Registration

6.1.1 Registration Requirements

Informed Consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and of its consent form is required.

6.1.2 CALGB Registration Procedures

This study uses the CALGB on-line Patient Registration system. Registration will be accepted only through CALGB Main Member institutions, selected affiliate

institutions, and CCOPs using the on-line Patient Registration system. Registration must occur prior to the initiation of therapy.

Confirm eligibility criteria (see Sections 4.0 & 5.0). Complete the Registration Worksheet. Access the on-line Patient Registration system via the patient registration icon on the CALGB Information Systems (IS) Application main menu. If the registering CRA requires assistance, he/she may consult the on-line help file located under the Help menu of the CALGB IS Application. If further assistance is required, the registering CRA may call the CALGB Registrar (919-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time; registration fax: 919-668-9397). Enter the following information:

Study

Name of group (CALGB)

Name of institution where patient is being treated

Name of treating physician

Name of treating physician or responsible CRA

Other group patient ID #, if applicable

CALGB patient ID #, if applicable

Patient's initials (last initial, first initial, middle initial)

Patient's Social Security #, date of birth, and hospital ID #

Patient's gender

Patient's race

Type of insurance (Method of Payment)

Disease, type and stage, if applicable

Patient's Postal Code, if applicable

Treatment start date

Date of signed consent

Date of signed HIPAA authorization

Patient demographics, if applicable

Companion studies (please see registration to companion studies, below)

Eligibility criteria met (no, yes)

When the patient is registered, a patient identification number will be generated. Please write the number in your records.

The Main Member Institution and registering institution will receive a Confirmation of Registration. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Hock Plaza, Suite 802, 2424 Erwin Road, Durham, NC 27705.

6.1.3 BMT CTN Registration Procedures

Patients enrolled through the BMT CTN will be registered and enrolled using the BMT CTN Electronic Data Capture System (AdvantageEDC™). An Authorized user at the transplant center will complete patient eligibility screening by entering patient demographics and completing the study Enrollment Form in AdvantageEDC. The patient's registration information will be automatically sent via e-mail to the CALGB Statistical Center. The patient's CALGB identification number will be generated and sent to the transplant center via e-mail.

6.2 Data Submission:

Forms should be submitted to the appropriate cooperative group in compliance with the data submission schedule below. This study will use NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for routine toxicity reporting on study forms.

6.2.1 CALGB Institutions:

There are two options for submitting forms that use the Teleform barcode and cornerstones:

- the forms may be faxed to the Statistical Center at the number listed on the form. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.
- the forms may be mailed to the CALGB Statistical Center, Hock Plaza, Suite 802, 2424 Erwin Road, Durham, NC 27705. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

Supporting documentation for studies using Teleform can be faxed or mailed along with the Teleform forms.

6.2.2 BMT CTN Institutions:

Data for patients enrolled through the BMT CTN will be submitted via AdvantageEDC. Criteria for timelines for all study forms are detailed in the table below and in the Data Management Handbook and User's Guide. Forms that are not entered into AdvantageEDC within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into AdvantageEDC and integrated into the Data Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

6.2.3 Data Submission Table:

Form	Submission Schedule
C-1090 CALGB 100103 Eligibility Checklist C-1090 CALGB 100103 On-Study Form C-1006 Peripheral Blood and Bone Marrow Form C-1505 HLA Typing Form Pathology Reports*	At the time of registration.
C-1740 Chimerism Results Form** Institutional Chimerism Results Report	Submit at timepoints specified in Section 6.3
C-1091 CALGB 100103 Follow-up Form C-1092 CALGB 100103 Adverse Event Form C-664 Infectious Complications Form§ C-1006 Peripheral Blood and Bone Marrow Form Pathology Reports***	Submit for the following time periods: • Days -7 through +30; • Days +30 through +120; • Q 3 months for one year post transplant (Day +365); • Q 6 months post Day +365 for 2 years.
C-702 Donor Cell Product Form	Submit Days -7 through +30
C-400 CALGB: Long-Term Follow-Up Form C-1006 Peripheral Blood and Bone Marrow Form	• Q 6 months beginning 2.5 years post Day +365 for a maximum of 5 years from study entry.
C-1001 New Malignancy Form	At occurrence of new malignancy.
C-113 CALGB Notification of Death Form	At time of death‡.
C-1742 CALGB Confirmation of Lost to Follow-up Form	See form for submission instructions.

- * Legible copies of all institutional pathology, cytochemistry, immunophenotyping, and cytogenetic reports used for patient registration must be submitted with the pre-study forms to the Statistical Center, Data Operations.
- ** Chimerism testing should be performed at the time points identified in Section 6.3 and the results recorded on Form C-1740. Institutional chimerism reports should be submitted along with Form C-1740 to the CALGB Statistical Center, Data Operations.
- *** Legible copies of all institutional pathology, cytochemistry, immunophenotyping, and cytogenetic reports documenting response, relapse, or progression must be submitted to the Statistical Center, Data Operations.
- ‡ All deaths within two years following protocol treatment that are not due to disease progression should be reported as adverse events (see Section 15.1).
- § Submit only if patient has infection, otherwise omit.

Please refer to the CALGB web site to obtain up-to-date data forms for this study.

6.3 Chimerism Analysis

Institutional chimerism testing on peripheral blood will be performed at the following time points:

[From Donor]:

- Either before or after recipient registration

[From Recipient]:

- Prior to registration
- Day +30 (+/- 3 days);
- Between Day +90 and Day +100;
- Day +180 (+/- 7 days);
- Day +365 (+/- 7 days);
- At time of relapse.

The window of time for drawing peripheral blood post-transplant for the chimerism analysis is within one week of the prescribed day. Institutional chimerism reports will be sent when they become available to the CALGB Statistical Center, Data Operations (see Section 6.2.3).

7.0 REQUIRED DATA

Guidelines For Pre-Study Testing

To be completed within 16 DAYS before registration:

- All bloodwork, history & physical (HLA typing may be done in advance but should be confirmed 2-3 months prior to transplant).
- Bone marrow aspirate and biopsy.
- Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.

To be completed within 42 DAYS before registration:

- Any baseline exams used for screening, i.e., PFTs.
- Any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

Tests & Observation	Prior to Study	BIW to Day +28, Weekly to Day +100, Monthly to Day +365	Restaging*	Post-Treatment Follow-up**
History and Progress Notes	X	X	X	X
Physical Examination	X	X	X	X
Pulse, Blood Pressure	X	X	X	X
Height/Weight/BSA	X			
Performance Status	X	X	X	X
Toxicity Assessment		X	X	X
Laboratory Studies				
CBC, Differential, Platelets	X	X		X
Serum Creatinine, BUN	X	X		X
Creatinine Clearance	X			
Serum Electrolytes	X	X		
AST, Alk. Phos., Bilirubin	X	X		X
Total Protein, Albumin	X			
Urinalysis	X			
EKG	X			
Hepatitis screen†, CMV Ab‡, HIV, EBV‡, HSV-I‡	X			
CMV Ag or PCR		A		
MUGA	X			
PFT	X			
Tacrolimus Levels		D		
Serologies & HLA Typing (Donor & Recipient)	X			
Staging				
Chest x-ray, PA & Lateral	X			
Bone Marrow Asp & Bx	X		C	C
Chimerism Analysis (Section 6.3)	B	B	B	B

* Restaging will occur between Days +90 - +100 and +150 - +180, then q 3 months for the first year.

** After restaging, at least every 6 months for a maximum of 5 years from study entry.

† To include Hep B Core Ab, Hep B Surface Ag, and Hep C Ab.

‡ To include IgG.

A Weekly beginning on Day +7 through Day +100, then according to institutional guidelines.

B Chimerism testing to be performed for recipients prior to on Day +30 (+/- 3 days), between Day +90 and Day +100, on Day +180 (+/-7 days), on Day +365 (+/- 7 days), and at time of relapse. For donors, chimerism testing can be performed either before or after recipient registration. See Section 6.3.

C Bone marrow biopsy will be required with restaging between Days +90 - +100, between Days +150 - +180, then q 6 months for the first two years, and then PRN thereafter as indicated by abnormal CBC.

D Twice weekly beginning on Day -2 until Day +28, then weekly until Day +150.

8.0 TREATMENT PLAN

All therapy (including methotrexate and tacrolimus) and growth factor doses will be based on a corrected body weight as follows: ideal weight + 25% of the difference between ideal and actual weight (see Appendix I for ideal body weight). If the actual weight is > 150% of ideal, their actual weight will be capped at 150% of ideal weight (i.e., their corrected weight will be 112.5% of ideal). For patients whose actual weight is less than ideal, then use actual weight.

8.1 Preparative Regimen

- 8.1.1 Fludarabine 30 mg/m²/day IVPB over 30 minutes x 5 days on Days -7 through -3.
- 8.1.2 Busulfan 0.8 mg/kg IV over 2 hours q6 hours x 8 doses on Days -4 through -3.

8.2 Supportive Care Guidelines

Patients will be evaluated on an outpatient basis for evidence of toxicity, in particular graft vs. host disease (GVHD) and cytopenias.

8.2.1 GVHD Prophylaxis

- 8.2.1.1 Tacrolimus dosing is to be based on target serum levels of 5-10 ng/mL. **Serum levels are not to exceed 15 ng/mL.** Tacrolimus is to be initiated on Day -2 with a suggested starting dose of 0.03 mg/kg PO BID. Begin tapering between Day +90 to +120 in the absence of GVHD as tolerated with a goal of stopping by Day +150 to +180. The rate of taper will be adjusted for the presence of signs and symptoms of GVHD. In patients who are unable to take oral tacrolimus, the intravenous dose is generally 1/4 to 1/3 of the oral dose.

Please note that concurrent use of agents such as itraconazole, voriconazole or fluconazole (at doses > 200 mg) may inhibit the metabolism of tacrolimus, and thus increase tacrolimus levels. Hence, it is recommended to check tacrolimus levels twice weekly when these agents are initiated concurrently. In addition, the initial dose of tacrolimus may be decreased according to institutional policies.

- 8.2.1.2 Methotrexate 5 mg/m²/day IV on Days +1, +3, +6 and Day +11. Hydrate intravenously and induce diuresis. Methotrexate will be held if the serum creatinine > 3.0 mg/dL. If the creatinine level is > 1.5 mg/dL, then administer leucovorin 10 mg IV or PO q6 hours for four doses beginning 24 hours after methotrexate.
- 8.2.1.3 Rabbit antithymocyte globulin (Thymoglobulin) at 2.5 mg/kg/day IV over 6 hours x 3 doses on Days -4 through -2. Patients must be premedicated with acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO/IV, and methylprednisone 1 mg/kg at initiation and midway through thymoglobulin administration each day. After the first dose, subsequent administration of antithymocyte globulin may be infused over 4 hours.
- 8.2.1.4 Patients with progressive disease will have met the primary study endpoint and will be removed from protocol therapy. Such patients may receive additional treatment at the discretion of the investigator, although patients will be followed for survival and new primary malignancies.

- 8.2.2 **Mucosal Evaluation and Care:** Mucositis is expected to be very mild with this chemotherapy regimen. Stomatitis and esophagitis due to herpes virus may be confused with drug-induced mucositis and viral cultures should be obtained

frequently. Patients with a history of herpes simplex infection or seropositivity will receive prophylaxis according to institutional guidelines through Day +100. One regimen that may be used is acyclovir 200-400 mg PO TID Days -3 through Day +100. Valacyclovir 500 mg PO QD may be used instead of acyclovir. Prophylaxis may be extended beyond Day +100 at the discretion of the treating physician.

8.2.3 Candida Prophylaxis

Candida prophylaxis will occur according to institutional guidelines through Day +100. A suggested regimen is fluconazole or itraconazole 200-400 mg PO daily or voriconazole 200-300 mg PO twice daily (or 3-6 mg/kg IV q12 hours) on Days -2 through +100. Low dose amphotericin B (10-20 mg/day) IV also may be used.

8.2.4 Pneumocystis Pneumonia (PCP) Prophylaxis

PCP prophylaxis will occur according to institutional guidelines through Day +100. One regimen that may be used to prevent PCP is cotrimoxazole (Bactrim[®]) administered as one double strength tablet BID on 2 days weekly, beginning on Day +21 through Day +100. If, at this time, CD4 lymphocytes are $< 200/\mu\text{L}$, then prophylaxis should be continued until CD4 lymphocytes are $\geq 200/\mu\text{L}$. Patients allergic to cotrimoxazole should receive dapsone or inhaled pentamidine instead. In patients who develop chronic GVHD, PCP prophylaxis should be extended at the discretion of the physician.

8.2.5 CMV Infections: No routine prophylaxis for CMV will be initiated. Surveillance for CMV using CMV Ag (e.g., immunofluorescence) or CMV PCR (or Digene Hybrid Capture[®] assay or equivalent) is required weekly beginning on Day +7 through Day +100, and then according to institutional guidelines. Patients with positive CMV PCR or positive CMV Ag should receive treatment according to institutional practice. One regimen is ganciclovir 5 mg/kg IV BID x 14 days (or appropriate doses of valganciclovir or foscarnet).

8.2.6 EBV Monitoring: Because of the use of antithymocyte globulin in all patients, it is strongly recommended that Epstein Barr Virus (EBV) surveillance of peripheral blood be performed in the form of EBV DNA PCR monitoring. EBV DNA PCR monitoring should be performed at least every two weeks from neutrophil engraftment through Day +100. If the EBV DNA copy number exceeds 1000/mL on two consecutive samples, it is recommended that rituximab 375 mg/m² IV be given to prevent post transplant lymphoproliferative disease (PTLD). Further rituximab dosing should be based on responses to first dose as measured by a change in the EBV DNA copy number. Patients with a positive EBV DNA PCR and signs or symptoms possibly attributable to PTLN (e.g., fever, lymphadenopathy) should undergo a CT scan of the chest, abdomen, and pelvis to rule out PTLN.

8.3 Allogeneic Stem Cells – Collection from Donors

8.3.1 HLA-Identical Sibling Donors

8.3.1.1 HLA-identical sibling donors will be treated with G-CSF 10 mcg/kg subcutaneously daily on Days -5, -4, -3, -2 (and -1, if the initial collection is inadequate). G-CSF will continue throughout mobilization, but will be reduced by 50% if WBC $> 50,000/\mu\text{L}$.

8.3.1.2 On Day -1 HLA-identical sibling donors will have vein to vein apheresis. CD3 and CD34 cells as fractions of the peripheral mononuclear (PMN) cells will be determined from the established PMN cell collection according to institutional flow cytometry. If the yield of CD34+ cells is less than $2 \times 10^6/\text{kg}$ (actual weight - recipient) on Day -1, an additional apheresis will be performed on Day 0 to achieve a minimum total CD34+ cell dose of $2 \times 10^6/\text{kg}$ (actual weight - recipient). Target CD34+ cell doses will be based

on institutional guidelines as long as they exceed 2×10^6 /kg. There is no maximum CD34+ cell dose.

8.3.1.3 The PMN cells will be separated and collected, while all the other separated blood components will be returned to the donor.

8.3.1.4 Cells from the stem cell collection either may be stored frozen or collected fresh.

8.3.2 Matched Unrelated Donors

Collection of peripheral blood stem cells will be performed on Days -1 (and 0) according to existing NMDP collection center protocols (or equivalent for other registries). Donors that are unwilling or unable to have PBSC collected will not be eligible. Matched unrelated donors are not required to complete Section 17.0 (Donor Consent Form).

8.4 Allogeneic Stem Cells - Infusion to Recipients

8.4.1 On Days 0 (and +1) a minimum total cell dose of CD34+ cells of 2×10^6 /kg (actual weight - recipient) will be infused. There is no maximum CD34+ cell dose.

8.4.2 G-CSF 5 mcg/kg/day subcutaneously beginning on Day +12 and continuing until ANC $>1500/\mu\text{L}$ for two consecutive days or $> 5000/\mu\text{L}$ for one day. If the ANC subsequently falls to $< 1000/\mu\text{L}$ then resume G-CSF at 5 mcg/kg/day.

8.4.3 Patients will be monitored weekly for engraftment and toxicity. Samples for chimerism studies should be collected on Day +30 (+/- 3 days), between Day +90 and Day +100, on Day +180 (+/- 7 days), on Day +365 (+/- 7 days), and at time of relapse (see Section 6.3).

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

9.1 Tacrolimus

Tacrolimus may cause hypertension, renal insufficiency (usually reversible), seizures, liver function abnormalities, hemolytic uremic syndrome (rare), hyperglycemia, and hypomagnesemia.

Tacrolimus dose adjustments will be made to achieve target trough levels of 5-10 ng/mL. Serum levels are not to exceed 15 ng/mL.

9.2 Methotrexate

Methotrexate may cause mucositis and cytopenias. In the presence of worsening renal insufficiency or the development of effusions or ascites, the addition of leucovorin is permitted at the discretion of the physician (see Section 8.2.1.2). **If the creatinine is > 1.5 mg/dL, leucovorin 10 mg IV or PO may be given every 6 hours for four doses beginning 24 hours after methotrexate. Methotrexate will not be given if the creatinine is > 3.0 mg/dL. Individual doses of methotrexate will not be altered.**

9.3 Graft Versus Host Disease

It is expected that some patients will develop mild-moderate graft versus host disease. It is precisely this effect that may be associated with an antineoplastic outcome.

The diagnosis of acute graft versus host disease rests on clinical presentation (rash, diarrhea, liver function abnormalities) and histopathologic evidence via skin, gastrointestinal, or liver biopsy. Chronic GVHD is associated with rash, sicca syndrome, hepatitis. In addition grade 2-4 GVHD or extensive chronic GVHD will be treated with methylprednisone 2 mg/kg/day. The ultimate treatment approach, i.e.,

the addition of cyclosporine, tapering of immunosuppressive medications, etc., will be left to the discretion of the transplant or hematology/oncology physician according to institutional standard allogeneic guidelines for the management of these conditions. The following tables should be used for reporting these toxicities.

9.3.1 Clinical Grading of Acute GVHD

Organ Grade	Skin Changes	Bilirubin (mg/dL)	Gut Changes (diarrhea [ml/day])
0	No rash	< 2.0	None
1	Erythematous macular rash over <25% body surface	2 - < 3.0	>500 - ≤ 1000
2	Over 25-50% of body surface	≥ 3 - < 6	> 1000 - ≤ 1500
3	≥50% body surface	≥ 6 - < 15	> 1500
4	Bullae, exfoliation ulcerative dermatitis	≥ 15	Severe abdominal pain with or without ileus

Organ Grade (see table above)			
Skin Changes	Hepatic	Gut Changes	OVERALL GRADE
0	0	0	0
1 or 2	0	0	1
1, 2, 3	1	1	2
2 or 3	2 or 3	2 or 3	3
Patients with Grade 4 toxicity in any organ system are considered overall Grade 4.			

9.3.2 Clinical Grading of Chronic GVHD

9.3.2.1 Limited Chronic GVHD:

1. Localized skin involvement, **and/or**
2. Hepatic dysfunction due to chronic GVHD.

9.3.2.2 Extensive Chronic GVHD:

1. Generalized skin involvement, **or**
2. Localized skin involvement and/or hepatic dysfunction due to chronic GVHD

Plus

- 3a. Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, **or**
- 3b. Involvement of eye (Schirmer's test with less than 5 mm wetting), **or**

- 3c. Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, **or**
- 3d. Involvement of any other target organ.

9.4 Instructions for Dosing by Corrected Body Weight

High-dose chemotherapy can adversely impact the outcomes of obese patients when dosing is performed according to actual body weight. **Therefore, all therapy (including methotrexate and tacrolimus) and growth factor drug doses will be determined using a corrected body weight formula.** Patients' ideal body weight will be derived from Appendix I using frame size and height. **The corrected body weight is calculated based on the following formula with all weights in kg:**

$$\text{Corrected Weight} = (0.25)(\text{actual weight} - \text{ideal weight}) + (\text{ideal weight})$$

Thus, for patients whose actual weight is >150% of ideal, their "actual" weight will be capped at 150% of ideal (i.e., their corrected weight will be 112.5% of ideal). For patients whose actual weight is less than ideal, use their actual weight as the corrected weight.

10.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

- 10.1** Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.
- 10.2** Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (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.
- 10.3** The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.
- 10.4 Fludarabine Monophosphate (Fludara®)**

AVAILABILITY

Fludarabine monophosphate is commercially available as FLUDARA IV as a white, lyophilized powder. Each vial contains 50 mg of fludarabine phosphate, 50 mg of mannitol and sodium hydroxide to adjust pH. Store at 15-30°C (59-86°F). Please refer to the agent's package insert for additional information.

STORAGE & STABILITY

Reconstituted FLUDARA IV is chemically and physically stable for 24 hours at room temperature or 48 hours if refrigerated. In addition, reconstituted FLUDARA IV contains no antimicrobial preservative and thus care must be taken to assure the sterility of the prepared solutions and should be discarded eight hours after initial entry.

PREPARATION

FLUDARA IV should be prepared for parenteral use only by aseptically adding Sterile Water for Injection, USP. When reconstituted with 2 ml of Sterile Water for Injection, USP, each ml of the resulting solution will contain 25 mg of Fludarabine Phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7-8.5. The product may be further diluted for intravenous administration to a concentration of 1 mg/ml in 5% Dextrose for Injection USP or in 0.9% Sodium Chloride, USP.

ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Fludarabine will be delivered as a piggy-back via an ongoing IV line, over a period of 30 minutes.

TOXICITY

Myelosuppression (dose limiting toxicity), fever, nausea, vomiting, stomatitis, diarrhea, gastrointestinal bleeding, anorexia, edema, skin rashes, myalgia, headache, agitation, hearing loss, transient episodes of somnolence and fatigue, autoimmune hemolytic anemia, autoimmune thrombocytopenia, paresthesias, peripheral neuropathy, renal and pulmonary toxicity (interstitial pneumonitis). Severe fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status were encountered almost exclusively after very high doses of fludarabine monophosphate. Such toxicity has only been rarely demonstrated at the 25-30 mg dosage of fludarabine monophosphate. Very rarely described complications include transfusion-associated graft versus host disease, thrombotic thrombocytopenic purpura, and liver failure. Tumor lysis syndrome, complicating fludarabine monophosphate therapy has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed in both pre-treated patients receiving fludarabine and in individuals receiving fludarabine combined with other agents (corticosteroids, mitoxantrone, and cyclophosphamide).

10.5 Tacrolimus (Prograf®)*AVAILABILITY*

Tacrolimus is a commercially available macrolide compound with potent immunosuppressant properties. Tacrolimus is available for oral administration as capsules containing the equivalent of 0.5 mg, 1 mg, or 5 mg of anhydrous tacrolimus. For IV use, tacrolimus is available as a sterile solution in 1mL ampules containing the equivalent of 5 mg of anhydrous tacrolimus per mL.

The oral absorption of tacrolimus is erratic and incomplete; absolute bioavailability is approximately 25%; peak serum levels are seen 1 to 3 hours after an oral dose, and therapeutic trough blood concentrations have ranged from 5 to 20 ng/mL; tacrolimus is extensively metabolized in the liver, with only small amounts of unchanged drug (2% or less) being recovered in the urine; the elimination half-life of tacrolimus is approximately 10 hours.

Tacrolimus suppresses both humoral (antibody) and cell-mediated immune responses. The compound is chemically distinct from cyclosporine but both agents elicit similar immunosuppressant effects. The immunosuppressive activity of tacrolimus is, however, more marked than that of cyclosporine.

Please refer to the agent's package insert for additional information.

PREPARATION -- FOR IV USE

Tacrolimus concentrate for injection must be diluted prior to IV infusion. For IV infusion, the concentrate is diluted with 0.9% sodium chloride or 5% dextrose injection to a concentration of 4-20 $\mu\text{g}/\text{mL}$. Preparation of the solution in polyethylene or glass containers allows storage for 24 hours beyond which unused solution should be discarded. A plasticized polyvinyl chloride (PVC) container should not be used because stability of the solution is decreased and polyoxyl 60 hydrogenated castor oil contained in the formulation may leach phthalates from PVC containers. Tacrolimus concentrate for 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

Tacrolimus is to be initiated on Day -2. Begin tapering between Day +90 to +120 in the absence of GVHD as tolerated with a goal of stopping by Day +150 to +180. See protocol text for tapering instructions, and for instructions for patients who are unable to take oral tacrolimus.

STORAGE & STABILITY

Store tacrolimus capsules at controlled room temperature, 15-30°C (59-86°F) (Prod Info Prograf®, 1997). An extemporaneous suspension of tacrolimus with a final concentration of 0.5 milligrams/milliliter was stable for 56 days when it was stored at 24-26°C in glass or plastic amber prescription bottles.

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. Mild to moderate hypertension was reported in 38% to 50% of patients receiving tacrolimus. Mild to moderate hypertension is a common adverse effect associated with tacrolimus therapy. Chest pain was reported in 19%. 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 a dosage reduction. Agitation, anxiety, confusion, seizures, depression, hallucinations, myoclonus, neuropathy, psychosis, incoordination, and abnormal dreams have been reported in 3% to 15% of tacrolimus-treated patients. Hyperkalemia (13% to 45%), hypokalemia (13% to 29%), hypophosphatemia (49%), and hypomagnesemia (16% to 48%) have been associated with tacrolimus therapy. In addition, hirsutism occurs only rarely with tacrolimus. Hyperuricemia has been reported in greater than 3% of tacrolimus-treated patients. Gastrointestinal adverse effects of tacrolimus have included nausea (32% to 46%), vomiting (14% to 29%), anorexia (7% to 34%), constipation (23% to 35%) and diarrhea (37% to 72%). Gingival hyperplasia observed in patients treated with cyclosporine has not been reported with tacrolimus therapy. Nephrotoxicity was reported in 36% to 40% and 52% of liver and kidney transplant patients receiving tacrolimus. Overt nephrotoxicity is usually seen early after transplantation and is characterized by an increased serum creatinine and a decrease in urine output. Hematuria has been reported in greater than 3% of tacrolimus-treated patients (Prod Info Prograf®, 1997). Abnormal liver function tests have been reported in 6% to 36% of patients receiving tacrolimus; ascites was reported in 7% to 27% of these patients.

Other miscellaneous effects that have occurred in clinical trials include pain (24% to 63%), fever (19% to 48%), asthenia (11% to 52%), back pain (17% to 30%), and peripheral edema (12% to 36%). The incidence of hyperglycemia is 17% and may require therapy with insulin. Other less frequently occurring effects (greater than 3%) include abscess, chills, peritonitis, and photosensitivity reactions. Anaphylaxis has been reported in a few patients receiving intravenous tacrolimus. Tacrolimus contains castor oil which has been associated with anaphylaxis in other drugs containing castor oil derivatives.

The incidence of bloodstream infection is 22%. Most infections are due to bacteria (81%), followed by candidemia (14%), and cryptococemia (5%). The source of bloodstream infection was primarily intravascular catheter, accounting for 39% of cases.

10.6 Methotrexate (Amethopterin®; MTX)

AVAILABILITY

Commercially available in 2 mL, 4 mL, 8 mL, 10 mL vials, or 1 g vials or preserved with benzyl alcohol. Please refer to the agent's package insert for additional information.

PREPARATION

The 1 gm vial may be diluted in 100 mL of saline or D₅W.

COMPATIBILITY

Additive incompatibility: bleomycin, prednisone.

STORAGE & STABILITY

Stability and compatibility of methotrexate sodium solutions depend on several factors including the formulation of methotrexate sodium used, presence of preservatives, concentration of drug, specific diluents used, resulting pH, and temperature; the manufacturer's labeling and specialized references should be consulted for specific information. Methotrexate sodium solutions should be inspected visually for particulate matter and discoloration whenever solution or container permits.

ADMINISTRATION

Administer via slow IV push. Hydrate intravenously and induce diuresis.

TOXICITY

Hematologic including leukopenia (1.5%), thrombocytopenia (5%; nadir 5-12 days; recovery 15-27 days), anemia (nadir 6-13 days), pancytopenia (1.5%); gingivitis, glossitis, pharyngitis, stomatitis, enteritis; nausea/vomiting, anorexia, diarrhea; hematemesis, melena; acute and chronic hepatotoxicity; transaminases increase 1-3 days after administration, hepatic fibrosis and cirrhosis with long-term therapy; pulmonary toxicity including pneumonitis, pulmonary fibrosis that is not dose-dependent and may not be fully reversible; pruritis, urticaria, photosensitivity; CNS: drowsiness, blurred vision, tinnitus, malaise, seizures; nephropathy: cystitis, dysuria, azotemia, hematuria, renal failure; diabetes; when administered it may cause headache, back pain, rigidity.

DRUG INTERACTIONS

Aminoglycosides may cause decreased absorption of methotrexate, and increased renal toxicity. Folic acid may decrease response to methotrexate. The use of NSAIDs may increase methotrexate levels. Probenecid, salicylates, sulfonamides may increase therapeutic and toxic effect of methotrexate. Procarbazine can cause increased nephrotoxicity. Theophylline may increase plasma levels. Alcohol may result in increased hepatotoxicity. Thiazides may cause granulocytopenia. Food will delay absorption, and decreases methotrexate peak.

10.7 Filgrastim (r-met HuG-CSF, G-CSF: Granulocyte Colony-Stimulating Factor, Neupogen®)

AVAILABILITY

r-met HuG-CSF is commercially available in 1.0 and 1.6 mL vials containing 300 µg and 480 µg G-CSF, respectively. Please refer to the agent's package insert for additional information.

STORAGE & STABILITY

G-CSF is available as a sterile buffered protein solution and must be stored at 2-8°C. DO NOT ALLOW THE DRUG TO FREEZE.

ADMINISTRATION

Each vial should be entered only once, and the remainder of the vial discarded and not re-entered a second time. The daily dose should be injected subcutaneously in one or two sites. Standard dosing is 5 µg/kg daily as a subcutaneous injection. Higher dosing (10 µg/kg) will be used for donors in this protocol.

TOXICITY

Chills, nausea, anorexia, myalgias, bone pain, local injection site pain or inflammation, abnormal liver function tests, thinning of hair, and enlargement of the spleen. Rarely fluid retention and pericardial effusion. All of these are generally reversible when the drug is discontinued.

10.8 Busulfan (Busulfex®)

AVAILABILITY

Busulfan is commercially available as 60 mg/10 mL ampuls. Please refer to the agent's package insert for additional information.

PREPARATION

Dilute busulfan injection in 0.9% sodium chloride injection or dextrose 5% in water. The dilution volume should be ten times the volume of busulfan injection, ensuring that the final concentration of busulfan is ≥ 0.5 mg/mL.

STORAGE & STABILITY

Store unopened ampuls under refrigeration at 2°C to 8°C. The diluted solution is stable for up to 8 hours at room temperature (25°C) but the infusion must also be completed within that 8-hour time frame. Dilution of busulfan injection in 0.9% sodium chloride is stable for up to 12 hours at refrigeration (2°C-8°C) but the infusion must also be completed within that 12-hour time frame.

ADMINISTRATION

Intravenous busulfan should be administered via a central venous catheter as a 2-hour infusion every 6 hours for 2 consecutive days for a total of 8 doses.

TOXICITY

Severe myelosuppression with marrow ablation, alopecia, and mild nausea/vomiting are expected. Alopecia may not be completely reversible. Liver toxicity including severe or fatal veno-occlusive disease (<5%) may occur. Pulmonary toxicity is rare in this schedule. In combination with etoposide, busulfan causes severe mucositis, esophagitis, and possible enteritis. It is expected that patients will require mouth care including narcotic analgesia, and may require parenteral nutrition. In combination with etoposide, busulfan may cause skin toxicity including painful desquamation, and this may require local care and narcotic analgesia. Darkening of the skin may occur and may last several months. Seizures may occur (<5%). Busulfan causes immunosuppression and risk of opportunistic infection even after resolution of neutropenia. Busulfan is expected to cause nearly universal infertility in the doses used, although men may occasionally father children.

NURSING IMPLICATIONS

1. GI toxicities leading to alteration in nutritional status. Patients require daily mouth care regimen which may include narcotic analgesic and potentially parenteral nutrition.
2. Painful desquamation may require local care and narcotic analgesics.

10.9 Antithymocyte Globulin (Rabbit) (Thymoglobulin®; rabbit ATG)

AVAILABILITY

Antithymocyte globulin is commercially available as a lyophilized powder for reconstitution containing 25 mg per vial. Each vial of powder is supplied with 5 mL diluent.

STORAGE & STABILITY

Intact vials should be stored under refrigeration and protected from light. Do not freeze. Reconstituted solutions should be used within 4 hours. Further diluted solutions for infusion should be used immediately after dilution.

PREPARATION

Remove the ATG rabbit plus diluent from the refrigerator and allow them to reach room temperature prior to reconstitution. Reconstitute each 25 mg vial with 5 mL of the diluent provided (sterile water for injection, USP). Rotate the vial gently to dissolve the powder. The resultant solution contains 5 mg/mL of ATG rabbit. Withdraw the calculate dose and inject into D₅W or NS for IV infusion. The final concentration should be 0.5 mg/mL. The solution should be administered through a 0.22 micron filter.

ADMINISTRATION

ATG rabbit will be administered IV at a dose of 2.5 mg/kg/day for 3 days (on Days -4, -3, and -2). The first dose should be infused over at least six hours, and subsequent doses over at least 4 hours. Infuse through a 0.22 micron in-line filter. Acetaminophen 650 mg PO, diphenhydramine 25-50 mg PO/IV, and methylprednisolone 1 mg/kg IV should be administered at the initiation and midway through each antithymocyte globulin (rabbit) infusion to minimize infusion reactions.

TOXICITY

Infusion reactions such as fever and chills are common, occurring in more than 10% of patients. Steroids, antihistamines and acetaminophen will be given, as described above, to minimize infusion reactions. Hypersensitivity reactions, including anaphylaxis, occur less frequently and may also be minimized with steroids and antihistamines.

Immunosuppression from antithymocyte globulin (rabbit) is associated with an increase in opportunistic infections, including fungal, viral, and pneumocystis infections.

11.0 ANCILLARY THERAPY

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.

12.0 CRITERIA FOR RELAPSE

12.1 Time of Response Evaluation: For all patients not demonstrating disease progression, response status will be evaluated by bone marrow aspiration and biopsy at the following time points after allogeneic stem cell transplant:

- Between Day +90 - +100 and Day +150 - +180 following allogeneic stem cell transplantation.
- Patients will be followed at least every 6 months for the first two years, and then as necessary for a maximum of 5 years from study entry. Treating physicians may be prompted to perform bone marrow examinations because of an abnormal CBC.

12.2 Definitions of Relapse

Patients with increasing numbers of myeloblasts in two successive bone marrow examinations will be declared treatment failures.

Relapse will be defined according to the revised recommendations of the International Working Group (24) as any of the following:

- The reappearance of leukemia blast cells in the peripheral blood.
- >5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration).
- If there are no circulating blasts, but the marrow contains 5-20% blasts, a repeat bone marrow \geq 1 week later with >5% blasts is necessary to meet the criteria for relapse.
- The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

13.1 Disease Progression or Disease Persistence

Disease progression constitutes attainment of the primary endpoint. At that time, protocol therapy will be discontinued and patients may be treated at the discretion of the treating physician. Relapsing patients will be removed from protocol therapy and followed for survival and secondary malignancy.

13.2 Extraordinary Medical Circumstances

If, at any time, the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy in patient records.
- Follow the patient for survival, progression, relapse, and secondary malignancies.

14.0 STATISTICAL CONSIDERATIONS

The study was originally designed to evaluate the efficacy of the study regimen in the combined MUD and SIB populations. In the amended version of the protocol, the primary study population is the MUD population. Analysis of the combined populations will now be a secondary objective. It is noted that no interim analysis of the efficacy endpoint, per CALGB policy, has been carried out to date.

This study is designed in a manner that is similar to a traditional phase II clinical trial but with two-year DFS replacing response rate as the outcome measure. DFS is defined

as the time to relapse (as defined in Section 12.2) or time to death (due to any cause) from the time of registration. Specifically we will test the hypothesis $H_0: p \leq 0.20$ versus $H_1: p > 0.2$, where p denotes the probability of being disease free (i.e., no relapse per Section 12.2 and alive) for at least 2 years. The null value of 0.20 is near the lower 95% confidence bound on the two-year DFS of older patients from recent CALGB studies in AML (95% CI I 0.19-0.29). The alternative value p_1 is the value determined to be the minimal clinically important proportion for this non-myeloablative approach to be considered a worthwhile improvement over standard therapy. On this trial, p_1 will be set at 0.35, exceeding the historical upper confidence bound on the two-year DFS achieved by standard chemotherapy.

The study opened in 01/15/04 and was temporarily suspended to accrual in 12/29/08. A total of 68 patients were registered. Three patients were cancelled at the day of registration. Among the 65 remaining patients, there were 39 SIBs and 26 MUDs. It should be noted that the study was originally only open to SIBs. The study was amended on 10/15/09 to allow MUDs to be registered. A total of 8 SIBs were registered prior to this amendment. While the point estimate for the proportion of MUDs is 0.4 (=26/65) a more relevant estimate would be 0.45 (26/(65-8)). It is our belief, that the transplant community feels more comfortable with entering MUDs than when the study was first conceived. As such, we expect an increase in registration of MUDs. We conclude that it is reasonable to assume that going forward that between 50 to 60% of the patients registered to the study will be MUDs. Our goal is to evaluate $n=61$ MUDs and SIBS respectively. We expect that we need to accrue an additional 61 evaluable patients to reach this goal. To account for cancellations, the number of additional patients registered to the study may be as many as 68. The median monthly registration to the study over the last two years before the temporary suspension was 2.5 patients. It will take about 28 months to accrue 68 patients. As, we expect that there will be a 6 month ramp up period to get back to the projected accrual level, the projected time needed to register 68 patients is expected to be 34 (6+28) months. Once we have enrolled 61 evaluable to a given cohort (SIB or MUD), further accrual to that cohort will be suspended.

Given that the observation window is long, a single stage design will be employed. We will enter $n=61$ MUD patients with AML in CR1 with a type I error rate of at most 0.1. We will have a power of at least 0.9 to test $H_0: p \leq 0.20$ versus the local alternative $H_1: p = p_1 = 0.35$. In particular, if at least 17 of these 61 patients are disease-free for at least two years, we will conclude that, at the given level of significance, there is statistical evidence that the probability of two-year DFS exceeds 0.2 and that the new therapy is worthy of further study. The actual type I and II error rates are $\alpha=0.0879$ and $\beta=0.0945$, respectively.

As a secondary analysis, we will evaluate the DFS profiles of the two combined populations (DFS and SIBS) using the Kaplan-Meier estimator. The DFS profile is not expected to be dependent on MUD vs SIB. Given the small sample size, we will not have power to detect any discrepancy between the two populations as any discrepancy is expected to be small. Nevertheless, we will provide a comparison of the two profiles as a descriptive analysis.

Transplant related mortality (TRM) Monitoring Rule: This study will be monitored closely for TRM, defined as death within the first six months after transplant not secondary to relapse. Using standard transplant protocols in younger patients with AML in CR1, TRM would be around 20% and a level of 40% or above would be considered unacceptable.

We will monitor TRM in six stages. The stopping boundaries are presented in Table 1 below when n_i denotes the maximum number of patients to be accrued by the end of stage i and where r denotes the cumulative number of episodes occurred at any point during the study. The probability of stopping the study under the specified stopping rule is illustrated for $\pi=(0.15, 0.20, 0.25, 0.30, 0.35, 0.4)$, where π denotes the probability of TRM is presented in Table 2. The presented scheme will have a probability of at most 0.08 of stopping early if the true TRM probability is at or below the acceptable rate of $\pi=0.2$

and a probability of at least 0.93 of stopping the trial early if the true TRM probability is at or above the unacceptable rate of $\pi=0.4$.

Table 1

Stage	Maximum number of patients up to the stage (n_1)	Suspend trial if
1	11	$r \geq 5$
2	21	$r \geq 9$
3	31	$r \geq 12$
4	41	$r \geq 14$
5	51	$r \geq 17$
6	61	$r \geq 20$

Table 2

TRM Probability	0.15	0.20	0.25	0.30	0.35	0.40	0.45
Probability of Stopping	0.02	0.08	0.24	0.52	0.78	0.93	0.98

The report generated following the completion of each interim safety look (for TRM) will be presented to the CALGB Data and Safety Monitoring Board (DSMB). This report will also provide some basic demographic and accrual information. Given that the completion dates of the interim safety looks do not coincide with the semi-annual DSMB meetings, it would be administratively difficult to coordinate the conduct of the study with the DSMB. The purpose of these reports is to keep the DSMB informed of the conduct of the study (e.g., decisions taken based on the results from the interim safety looks). Needless to say, any recommendation from the DSMB will be carefully considered. Given that there is no interim analysis planned for the primary clinical endpoint of the study (DFS), interim summaries of the DFS or any other efficacy data, unless specifically requested by the DSMB, will not be included in these reports.

Pharmacokinetic Statistical Considerations

The primary objective of the pharmacokinetic (PK) companion study was to assess the discrepancy in the distribution in older patients compared to what has been reported for younger patients. This objective will be addressed using the samples already collected. As such, the companion study will not be reopened along with the clinical study. The statistical considerations provided for the PK analysis are provided below for reference.

For simplicity, we will assume that both of these distributions are normally distributed. Furthermore, we will assume that they share a common variance.

The mean clearance of busulfan has been reported in the literature as 2.74 mL/min/kg for the first of 16 doses of 0.8 mg/kg [22]. The standard deviations associated with that mean clearance is 0.82 mg/kg [22]. These values were derived from a patient population of $m=61$ patients with median age 37 years (range 20-63). Of those $m=61$ patients, 11 (18%) were between the ages of 50 and 63. Henceforth, for notational brevity, we will omit providing the units (i.e., mL/min/kg) for the mean and standard deviation. Using $\mu_0=2.74$ as the putative mean clearance for the population of younger patients, the hypotheses of interest may be canonically presented as testing $H_0: \mu_0=2.74$ versus the alternative $H_1: \mu_0 < 2.74$, where μ_0 denotes the mean clearance for the older patients.

A maximum of 61 patients are planned to be accrued to CALGB 100103. We expect to have at least $n=21$ patients (about one-third) for the pharmacokinetic analysis. Assuming that the clearances (log-transformed) are normally distributed, the smallest effect size (ratio of the difference in means and standard deviation) detectable with the t-test (with $n-1$ degrees of freedom) at the two-sided 0.05 level with a power of 0.9 is 0.744. Assuming that the standard deviation is 0.82, this corresponds to testing $H_0: \mu_0=2.74$ versus the local alternative $H_1: \mu_0=2.13$. This effect size is deemed to be clinically interesting as well as realistic.

We do point out that given the small sample size, the t-distribution may not adequately approximate the sampling distribution of the so called t-statistic if the distribution of the (log-transformed) clearances was to deviate considerably from that of a normal distribution. For simplicity, however, we have opted to employ the t-test instead of a non-parametric counterpart. We will conduct, if appropriate, resampling methods and compare those results with that obtained from the t-test. Furthermore, we point out that the reference mean and standard deviation used in these calculations are based on empirical estimates and are not the true values for these parameters.

If a large enough sample of assessable patients is obtained, we will explore potential associations between clinical response endpoints and PK parameters using logistic (for binary endpoints) and log-linear Cox (for censored time-to-event endpoints) regression models.

15.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. CALGB investigators are required to notify the CALGB Central Office, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event (follow guidelines in the table below). The description and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning October 1, 2010. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

All reactions in a “reportable” category must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS). Investigators are also required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols using the protocol adverse event form. Cases of secondary AML/MDS are to be reported to the CALGB Central Office using the NCI/CTEP Secondary AML/MDS Report Form. New primary cancers should be reported using CALGB Form C-1001.

CALGB requires investigators to route all adverse event reports (AERs) through the Central Office for CALGB-coordinated studies.

Note: BMT CTN Institutions

For most BMT CTN protocols, all grade 3-5, unexpected events are reported via the expedited reporting system in AdvantageEDC and all expected events, regardless of severity, are captured on scheduled and event-driven forms. For this protocol, however, the reporting requirements differ slightly in that grade 3, unexpected events are reported but not via expedited reporting, and grade 4 unexpected events that are at least possibly related to treatment, and all grade 5 events, both expected and unexpected, require expedited reporting via AdEERS. BMT CTN institutions will use the NCI Adverse Event Expedited Reporting System (AdEERS).

CALGB 100103 Adverse Event Reporting Requirements

Phase 2 and 3 Trials: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days¹ of the Last Dose of Treatment²

	Grade 1	Grade 2	Grade 3		Grade 3		Grade 4	Grade 4	Grade 5 ³	Grade 5 ³
	Unexpected and Expected	Unexpected and Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	24-Hrs; 5 Calendar Days	10 Calendar Days

¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
 AdEERS 24-hour notification followed by complete report within 5 calendar days for:
 • Grade 5 unexpected events
 AdEERS 10 calendar day report:
 • Grade 4 unexpected events
 • Grade 5 expected events

² Treatment is defined as protocol preparative regimen, GVHD prophylaxis, and stem cell infusion.

³ Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
 - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
 - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Grade 5 events must be reported via AdEERS within 24 hours/5 calendar days (unexpected and at least possibly due to treatment), or 10 calendar days (expected; unexpected and unlikely related to treatment).
- All grade 4 events that are unexpected and that are at least possibly related to treatment must be reported via AdEERS within 10 calendar days.
- Any unexpected medical event equivalent to CTCAE grade 4 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported via AdEERS within 10 calendar days.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials:

- A list of specific expected adverse events can be found in Section 9.0 (Drug Formulation, Availability, and Preparation).
- AdEERS reports are to be submitted electronically (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm) to the CALGB Central Office (CALGB@uchicago.edu). Faxed (312-345-0117) copies of the AdEERS paper template (downloadable from the AdEERS web page) will also be accepted, but electronic submission is preferred.
- All adverse events reported via AdEERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- The reporting of adverse reactions described in the tables above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (see Section 6.2 for required CALGB forms).
- All deaths within two years following protocol treatment that are not due to disease progression should be reported as adverse events.

16.0 REFERENCES

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17.0 DONOR MODEL CONSENT FORM

A Phase II Study of Allogeneic Transplant for Older Patients with AML in First Morphologic Complete Remission Using a Non-Myeloablative Preparative Regimen

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

[Attach NCI booklet “Taking Part in Clinical Trials: What Cancer Patients Need To Know”]

You have been identified as an HLA-identical sibling, that is a brother or sister who has the same type of bone marrow and can therefore serve as a good donor of bone marrow or “stem cells” for a family member who has been diagnosed with leukemia.

[Reference and attach information about the type of cancer (and eligibility requirements, if desired).]

WHY IS THIS STUDY BEING DONE?

You are being asked to take part in this study because you have a sibling that has been diagnosed with acute myeloid leukemia, a form of cancer that originates from the lymphocytes, the cells that make up the immune system and that are located in the lymph nodes, bone marrow and most of the other organs of the body. Unlike other forms of leukemia, these cancers are often difficult to treat with standard forms of treatment such as chemotherapy.

A transplant of some of sibling’s bone marrow or “stem cells” may be effective treatment for these cancers. Stem cells are the original cells from which all the blood cells (including white blood cells which help fight infection, red blood cells which carry oxygen, and platelets which help the blood to clot) develop. The use of high doses of chemotherapy to kill cancer cells in patients, along with the use of stem cells from a healthy sibling donor such as yourself, may improve the outcome of patients with this disease.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 136 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will undergo blood tests to insure that you do not carry any communicable diseases that could be transmitted through your blood (such as hepatitis, HIV, etc.). Other tests to determine your suitability as a donor may be necessary, as well.

Treatment

It is possible to stimulate the bone marrow to produce stem cells with a drug called filgrastim, also known as G-CSF. G-CSF is a commercially available and approved medication used in patients receiving chemotherapy for cancer to increase the number of white blood cells, the cells responsible for fighting infections. When G-CSF is given to a healthy brother or sister who has been shown to have the same type of bone marrow as the patient with cancer, it is possible to obtain a collection of stem cells that can then be used to rescue their siblings who have cancer and are undergoing high dose chemotherapy. The stem cells collected from the donor (that is, a brother or sister) may also aid in recognizing and destroying any cancer cells that may still be in the patient's body after the high dose chemotherapy.

G-CSF will be given to you, the donor, for four to five consecutive days as a daily injection just underneath the skin (subcutaneous injection). We will teach you or a family member to give you the injections at home. During the four-day period in which you are receiving G-CSF, your white blood cell count will increase. After the fourth day, a process known as leukapheresis will be performed where the stem cells will be taken from the blood stream of the donor.

The leukapheresis procedure is similar to the process of blood donation, where a needle is placed in the vein of the arm and blood is removed in a sterile fashion. In leukapheresis, the blood is removed and filtered (centrifuged) so that only the white blood cells, stem cells, and some plasma are removed. About one-half pint of blood cells are collected for the transplant. The rest of the blood (mostly red blood cells) is returned back into the blood stream of the donor through a second needle. The leukapheresis procedures will be performed on the fifth day and, possibly, the sixth day after you have been receiving G-CSF. Each collection of stem cells will then be transfused directly into the patient (your brother or sister) who in the meantime will have received high dose chemotherapy.

A daily check of your blood counts will be performed on the days when you are undergoing leukapheresis. This will require about 1-2 teaspoons to be removed by blood draw from one of your veins.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for approximately 5-6 days.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your brother or sister's doctor first. There may be no consequences to your health if you discontinue participation in this study, but it may have serious affects on the recipient (that is, your brother or sister) if they have already received chemotherapy for their transplant.

[Describe any serious consequences of sudden withdrawal from the study.]

WHAT ARE THE RISKS OF THE STUDY?

A daily check of your blood counts will be performed on the days when you are undergoing leukapheresis. The risks of the blood draw include bruising, inflammation in the vein, and infection. Care will be taken to avoid these complications.

The most common side effect of G-CSF is bone pain as the bone marrow becomes active. This is not common but can be relieved with acetaminophen (Tylenol[®]) in most cases. Other rare side effects which have been described or reported include bruising at the injection sites, fever, nausea, vomiting, diarrhea, headache, skin rash, chest pain, hair loss, loss of appetite, shortness of breath, enlarged spleen, drop in blood pressure, and generalized weakness. All of these side effects go away when the G-CSF treatment is stopped.

The risks and side effects of the leukapheresis process have to do with the placement of the leukapheresis needles in the veins of the arms. These risks are similar to those involved in blood donation and include nausea, vomiting, dizziness, seizures (if you faint), blood loss, inflammation in the vein and infection. Also, with the leukapheresis process, the platelet count (the cells partly responsible for blood clotting) may drop. This drop in blood counts is temporary and should return to normal within one or two days.

Risk of Testing for Infectious Illnesses: Participation in this study will require that you be tested for hepatitis and HIV. Testing for HIV and for the hepatitis viruses may result in a diagnosis of infection with these viruses. In the event that you are diagnosed with hepatitis or HIV, you may be referred to a doctor who specializes in these illnesses. The diagnosis of HIV or hepatitis may result in earlier treatment and/or prevention of many complications from the illnesses. Efforts will be made to keep your personal information confidential. Awareness of a diagnosis of these illnesses may have serious personal and social consequences. Some of these consequences include possible difficulty obtaining health insurance or employment.

For more information about risks and side effects, ask the researcher or contact

[Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks.]

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Although there is no direct benefit to the donor, the stem cell transplant is potentially life-saving to the recipient who is suffering from an otherwise fatal cancer.

WHAT OTHER OPTIONS ARE THERE?

Your participation in this study is voluntary.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research and medical records for quality assurance and data analysis include groups such as:

- Cancer and Leukemia Group B
- Blood and Marrow Transplant Clinical Trials Network
- National Cancer Institute
- Food and Drug Administration

WHAT ARE THE COSTS?

The cost of the G-CSF medication and the leukapheresis procedure will be billed to you and your insurance company or your sibling's insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You, your insurance company, or your sibling's insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher NAME(S) at TELEPHONE NUMBER.

For questions about your rights as a research participant, contact the NAME OF CENTER Institutional Review Board (which is a group of people who review the research to protect your rights) at TELEPHONE NUMBER. *[And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI's Web sites...

CancerTrials: comprehensive clinical trials information
http://www.cancer.gov/clinical_trials

CancerNet™: accurate cancer information including PDQ
http://www.cancer.gov/cancer_information

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

[Attach information materials and checklist of attachments. Signature page should be at the end of package.]

SIGNATURE

I agree to take part in this study.

Participant _____ Date _____

18.0 RECIPIENT MODEL CONSENT FORM

A Phase II Study of Allogeneic Transplant for Older Patients with AML in First Morphologic Complete Remission Using a Non-Myeloablative Preparative Regimen

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

[Attach NCI booklet “Taking Part in Clinical Trials: What Cancer Patients Need To Know”]

You are being asked to take part in this study because you have acute myeloid leukemia.

[Reference and attach information about the type of cancer (and eligibility requirements, if desired).]

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) this treatment has on you and your type of cancer.

This research is being done to improve the outcome of patients diagnosed with acute myeloid leukemia who may have achieved a complete remission with their initial therapy.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 136 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Medical Tests

The following tests must be done to make sure that you are eligible for this study. None of these tests are experimental. They are routine. Depending on when you last had them, you may need to repeat some of these tests:

- Blood tests
- Chest x-ray
- Urinalysis
- EKG
- Pulmonary Function Tests (PFT)
- Echocardiogram or MUGA (a heart scan)
- Hepatitis, HIV Test

- Bone marrow aspirate and biopsy

Many of these tests will be repeated during the study. If you participate in this study, some of these tests may be done more frequently than if you were not taking part in this research study.

Studies to evaluate how well your body has accepted the blood cells from your donor will be performed. These studies are part of routine care for patients undergoing transplantation. The blood and bone marrow samples will be collected prior to beginning treatment on this study, and 30, 90, 180, and 365 days following your transplant. A final sample may be required after all treatment has been completed, or if your disease should return. The samples will be collected only when routine blood and bone marrow are collected for the purposes of following your response to treatment. Therefore, you will not have to undergo any additional procedures to collect these samples and you will not be at any additional risk for complications from these procedures.

Treatment

The standard treatment for your disease is chemotherapy. The treatment on this research study is a new approach that attempts to stimulate your own immune system to fight your disease. The chemotherapy given to you during treatment is meant to weaken your immune system (the white blood cells responsible for fighting infections) in preparation of the introduction of the red blood cells and immune cells from your donor. The goal of this study is to replace the defective cells responsible for your disease with normal cells from your donor. If you agree to participate, you will receive the chemotherapy drug fludarabine by intravenous (IV) infusion over 30 minutes each day for five (5) days one week before you receive your donor's cells. Fludarabine will be given to you by IV infusion through a needle in a vein in your arm or through a "central line" which is an IV catheter (or tube) placed in the large vein under your collarbone or your neck. The day you receive your donor's cells will be known as Day 0 or the day of transplant. Thus, fludarabine will be given on Day -7 through Day -3 (that is, fludarabine will be given for five days, one week before Day 0). Another chemotherapy drug known as busulfan will be given for two days by IV infusion every six hours (for a total of eight doses) on Day -4 through Day -3 (that is, busulfan will be given for two days, beginning four days before Day 0). Thymoglobulin, another drug intended to weaken your immune system in preparation for your donor's cells, will be given on Days -4 through Day -2 (that is, thymoglobulin will be given for three days, beginning four days before Day 0). You will also receive the drug known as tacrolimus beginning on Day -2 through approximately Day +150 (that is, approximately 5 months after Day 0). Another chemotherapy drug called methotrexate will be given on Day +1, +3, +6, and +11. On Day 0, the day of transplant, you will receive what are known as "stem cells" (cells which will eventually develop into white blood cells, red blood cells and platelets) from your donor. After Day 0, you will be given antibiotics to help fight

infections; blood transfusions to increase the number of red blood cells in your system; platelet transfusions to assist in helping your blood to clot; and nutritional and general support. Finally, on Day +12 you will receive the drug G-CSF daily by subcutaneous injection (that is, an injection under your skin) until your blood counts have recovered to satisfactory levels. G-CSF will help to stimulate white blood cell production.

HOW LONG WILL I BE IN THE STUDY?

For the first 28 days on this study, you will be seen frequently by your doctors and have lab tests drawn at least twice weekly. You will then need to be seen by your doctor and have lab tests drawn at least once weekly for the next 100 days, and then every month for the first year. Following the first year, you will need to be seen and have lab tests drawn at least every three months for a year and then every six months for a maximum of five years from the date of entry on the study.

The researcher or your regular doctor may decide to take you off this study if:

- Your cancer returns and does not respond to the treatment that is part of this study.
- Your health gets worse.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on this study, you are at risk for these side effects. You should discuss these with the researcher and/or your doctor. Other drugs may be given to you to make side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long-lasting, or permanent.

Since performing a donor stem cell transplant in patients aged 60 and over using a less intensive chemotherapy approach is experimental, there may be significant toxicities associated with this approach and there may be side effects that we cannot predict. Some side effects could be so serious that they may result in your death.

Risks associated with this treatment include:

Likely:

- Lowered white blood cell count[®] that may lead to infection.
- Lowered platelets[®] which may lead to an increase in bruising or bleeding.

- Lowered red blood cells^v which may cause anemia, tiredness, or shortness of breath.
 - Fever, chills.
 - Diarrhea, nausea, vomiting.
 - Increased risk of infection.
 - Loss of appetite and/or weight loss.
 - Weakness, fatigue and dizziness
 - Muscle aches.
 - Rash, itching.
 - Elevated liver function tests.
 - Time away from work.
 - Partial hair loss.
 - Painful burning of the skin on hands and feet.
- ^v Should this occur, it can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of chemotherapy given to you.

Less Likely But Serious:

- Rejection of your donor's stem cells
- Graft versus host disease (see below)
- Sterility
- Kidney damage (may be permanent).
- Lung damage (may be permanent).
- Liver damage (may be permanent).
- Hives, including severe rash leading to skin loss and mucous membrane damage.
- Bleeding from your stomach or intestines.
- Red blood cell destruction by the immune system. Blood may be present in your urine.
- Incoordination or a temporary unsteadiness when walking.
- Hypertension (high blood pressure) which may require treatment.
- Chest pain.
- Heart damage (may be permanent).

- Hearing loss (may be permanent).

WHAT IS GRAFT VERSUS HOST DISEASE (GVHD)?

GVHD is a side effect of bone marrow or stem cell transplantation. In cases of GVHD, the new donor cells treat your body as “foreign” and launch an attack against it. The most common sites of attack by cells causing GVHD are the skin, liver, and gastrointestinal tract. If it occurs within 100 days after transplant it is called acute GVHD. If it occurs later it is called chronic GVHD. Symptoms of GVHD can range from mild to severe, and when severe GVHD can be fatal (cause death). Medications are given in this study to prevent or reduce the chances of having severe GVHD, and to treat GVHD if it occurs.

Symptoms of GVHD that may occur include:

- Skin rash
- Liver disease (including jaundice)
- Nausea, vomiting, diarrhea
- Temporary darkening of the skin and hardening and thickening of patches of skin and tissue under the skin (occurs with chronic GVHD)
- Dry and sore mouth and eyes (chronic GVHD)
- Bacterial, fungal, and viral infections (acute and chronic GVHD)
- Weight loss
- Lung disease (chronic GVHD)

The risk of developing moderate to severe GVHD following transplantation of stem cells from a matched related donor is between 30-50%. GVHD usually begins when your donor’s stem cells begin to make blood cells. The cell that is felt to be responsible is a type of white blood cell known as a T-cell. You will receive medications to reduce the chance that donor T-cells will attack your body to reduce the risk or prevent GVHD. These drugs can cause an increased susceptibility to infection.

A small amount of GVHD may be beneficial if the T-cells attack any remaining leukemia cells and destroy them.

Less Likely But Not Serious:

- Tingling of the fingers and/or toes.
- Weight gain and/or swelling.
- Insomnia.

Reproductive risks: The drugs used in this study are known to have risk of causing malformations in an unborn child. Therefore, you should not father a baby while on this study. For this reason, men will be asked to practice an effective method of birth control while participating in this study. Ask about counseling and more information about preventing pregnancy.

Risk of Testing for Infectious Illnesses: Participation in this study will require that you be tested for hepatitis and HIV. Testing for HIV and for the hepatitis viruses may result in a diagnosis of infection with these viruses. In the event that you are diagnosed with hepatitis or HIV, you may be referred to a doctor who specializes in these illnesses. The diagnosis of HIV or hepatitis may result in earlier treatment and/or prevention of many complications from the illnesses. Efforts will be made to keep your personal information confidential. Awareness of a diagnosis of these illnesses may have serious personal and social consequences. Some of these consequences include possible difficulty obtaining health insurance or employment.

Secondary Malignancy: A number of established chemotherapy agents have an inherent risk of causing another cancer (secondary malignancy). Certain drugs in use today, not currently known to be associated with this risk, may be shown at a later time to result in the development of these secondary malignancies

For more information about risks and side effects, ask the researcher or your doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with acute myeloid leukemia in the future.

WHAT OTHER OPTIONS ARE THERE?

You may receive treatment for your type of cancer without being on this study. Instead of participation in this study, you have these options:

- No therapy at this time with care to help you feel more comfortable.
- Treatment with other commonly-used chemotherapy.
- A bone marrow transplant without participating in this study.

You may get the same treatment in this clinical trial at this center and other centers even if you do not take part in the study.

Please talk to your doctor about these and other options.

[Reference and attach information about alternatives.]

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research and medical records for quality assurance and data analysis include groups such as:

- Cancer and Leukemia Group B
- Blood and Marrow Transplant Clinical Trial Network (BMT CTN)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person:
(name)_____ (title)_____
(address)_____ (phone
number)_____.

WHAT ARE THE COSTS?

The drugs used in this study are commercially available and will be charged to you and your insurance. You and your insurance company will be responsible for all costs related to the study treatment. Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher NAME(S) at TELEPHONE NUMBER.

For questions about your rights as a research participant, contact the NAME OF CENTER Institutional Review Board (which is a group of people who review the research to protect your rights) at TELEPHONE NUMBER. *[And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI's Web sites...

CancerTrials: comprehensive clinical trials information
http://www.cancer.gov/clinical_trials

CancerNet™: accurate cancer information including PDQ
http://www.cancer.gov/cancer_information

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

[Attach information materials and checklist of attachments. Signature page should be at the end of package.]

SIGNATURE

I agree to take part in this study.

Participant _____ Date _____

APPENDIX I

Ideal Body Weight Table

IDEAL BODY WEIGHT TABLE

	<u>Height</u> (Feet/Inch)	<u>Small Frame</u> (kg)	<u>Medium Frame</u> (kg)	<u>Large Frame</u> (kg)
MEN	5'2"	54	59	64
	5'3"	56	60	65
	5'4"	57	62	67
	5'5"	59	63	69
	5'6"	60	65	71
	5'7"	62	67	73
	5'8"	64	69	75
	5'9"	66	71	77
	5'10"	68	73	79
	5'11"	70	75	81
	6'0"	72	77	84
	6'1"	74	79	86
	6'2"	76	82	88
	6'3"	78	84	90
6'4"	79	86	93	
WOMEN	4'10"	45	49	54
	4'11"	46	50	55
	5'0"	47	51	57
	5'1"	49	53	58
	5'2"	50	54	59
	5'3"	51	55	61
	5'4"	53	57	63
	5'5"	54	59	64
	5'6"	56	61	66
	5'7"	58	63	68
	5'8"	59	65	70
	5'9"	61	67	72
	5'10"	64	69	74
	5'11"	65	70	76
6'0"	67	72	79	